# A multilevel perspective of patients and general practitioners

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# *A multilevel perspective of patients and general practitioners*

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# Content

*Chapter 1*

# Introduction

***This study came about as a result of working together with general practitioners (GPs) and because of my interest in multilevel statistical techniques. As a methodologist for the Registration Network of Groningen (RNG), I contributed to the development of the longitudinal morbidity and medication registration programs used by the Department of General Practice Medicine in Groningen. The RNG was established and developed by the Department of General Practice Medicine at the University Medical Center in Groningen (UMCG). Besides for patient care, which is the RNG's primary purpose, these data are meant to be used for research, education, and to help determine future directions [1].***

The GPs who participate in the RNG have been collecting data since 1989. There are 17 GPs participating in the RNG: 3 in a solo practice and 14 in group practices. In 2008, the GPs from Groningen, 3 in solo practice and four in group practices, joined the University's 'General Practice Medicine' Group Practice. All of the participating GPs use the same GP information system MicroHIS. MicroHIS is used for all daily practice activities. Every patient contact is registered. The diagnosis, referral indications, and medications administered and prescribed are coded according to the International Classification for Primary Care (ICPC). For each episode, a diagnosis is registered. Medications are automatically coded according to the Anatomical Therapeutic Chemical Classification System (ATC). An 'episode of disease' is the period between the moment that a disease is clinically diagnosed until the moment that it has been determined the disease came to an end. In the GP practice, the term 'episode of care'[1-3] is used, which means: the period that starts from the first time the health problem is mentioned by the patient to the GP until the last contact with regard to this health problem.The end of the episode of care is not necessarily the end of the episode of disease. In this dissertation, the term 'episode', meaning 'episode of care', will be used. The amount of medication prescribed is recorded in terms of the 'Defined Daily Dose' (DDD). DDD is defined as the assumed average daily dose of a drug used for its main indication in adults.



The RNG's data structure is hierarchical; that is to say, the patients are nested under their GPs. This allows for a seamless application of multilevel techniques. The data collected in the general practices is always hierarchical. Differences among GPs and differences among patients are often studied. As a result, though much is known in these two areas of study, correlations between the two are not often described. Variability in the RNG data may exhibit a hierarchical structure, therefore any analysis of that data must take the structure into account [4].
Some studies [5-9] have tried to explain the variation among practitioners, but few conclusions have been drawn. It is not sufficient to identify the variables responsible. Multilevel methodology allows us not only to identify the variables, but also to quantify their contributions at different levels. Multilevel methodology will be described in chapter two as well as the different kinds of multilevel models (i.e. multilevel regression models) and the factors affecting the choice of multilevel model. The later chapters will be used to describe studies done with multilevel methodology using data obtained by the RNG and an insurance company.

Several research questions that are addressed and analyzed with multilevel modelling will be the topics addressed in the subsequent chapters.
In chapter three, we will look at how general practice and patient characteristics relate to appropriate prescribing habits as described in the Groningen Formulary.
In chapter four we will look at the workload of general practitioners in socio-economically challenged communities. In 1999, the Netherlands Institute for Health Services Research (NIVEL) fine tuned the methods used to identify such communities. In Groningen, four of the original eight postal code areas no longer met the criteria describing a socio-economically challenged community [10]. Because of this, we wanted to have a closer look at several aspects of health care in those areas. Specifically, we wished to address the research question: Does the care required by patients living in socio-economically challenged communities cause the GPs to have a heavier workload than GPs in other areas?
In chapter five, we illustrate that a hierarchical model is also well-suited to the analysis of a longitudinal data set. We do this by looking at how patient and morbidity characteristics are related to the amounts of antibiotics prescribed. The research questions in both chapters four and five are addressed using a longitudinal dataset.
In chapter six, a treatment control design is used to look at the effect on chronic users of benzodiazepines when their GP sends them a letter recommending reduction or cessation of benzodiazepine use. The research question here is: does a letter from their own family physician recommending decreasing or stopping the use of benzodiazepines lead to a decrease in actual use? In answering this question, we regard benzodiazepine use as a continuous variable, therefore, we will use a random effect regression technique. Vermunt[11,12] has shown that multilevel models which have a discrete heterogeneity may be used to identify discrete patient categories with the help of latent class models. For the research question dealing with antibiotic prescriptions, we used the latent class model method. Here, we will apply the multilevel latent class model.
In the 7$^{th}$ chapter, our main findings will be summarized along with a critical analysis of prior chapters. Conclusions will be drawn and recommendations with respect to future directions will be made. The techniques used for this thesis appear in the literature under various names, such as: mixed model, random coefficient model, covariance components model, and hierarchical linear model. With a longitudinal dataset, the terms ‘growth model’ and sometimes ‘individual growth model’ have also been used.
We will consistently use the term ‘multilevel’ throughout this manuscript. Although this dissertation is meant for a general audience, avoiding technical issues entirely is not possible. Such issues will, however, be discussed in a relatively non-technical way; technical details may be found elsewhere [13-21]. In the Appendix, a few topics are addressed which include some technical issues. This may interest some readers.

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*Chapter 2*

# *General approach*

**In this chapter we will describe multilevel methodology and introduce several different models. The advantages and disadvantages of multilevel techniques will be addressed and conclusions will be drawn.**

### *2.1 What is multilevel methodology?*

This thesis is concerned with studies of patients and doctors in general practice. We will be looking at the relationship between general practitioners (GPs) and patients from a health care perspective. The patients who are registered with a general practice form a cluster of individuals who add up to an administrative group. The health care needs of these patients are served by a single general practice and often by a single GP. In this situation, the patients are said to be nested under the GP, and in the case of group practices the GPs are nested under the practice; a hierarchical data structure results, defined by GPs and practices. This results in a complex pattern of variables when undertaking research. Multilevel models have been developed for analyzing such data[1-4]. The hierarchy we see here always has the patients nested under the GPs. Snijders and Bosker defined multilevel analysis as a methodology for the analysis of data with complex patterns of variability with a focus on nested sources of variability[4]. The term 'multilevel model' is used by many authors[1,3-20], but several other terms have also been used to describe this technique, such as 'hierarchical linear models' [21-23], and 'random coefficient models'[24,25].
One may state briefly that multilevel modelling, which includes hierarchical linear modelling, random coefficient modelling, variance, and covariance components models, is a form of hierarchical regression analysis which has been developing since the early 1980s, designed to handle hierarchical and clustered data.



For these types of studies, descriptive variables for both the GPs and the patients are important. Individual level variables characterize individuals and refer to individual level constructs. For instance, with respect to the patient, gender, age, and socio-economic status are variables that describe individual patients. Example variables for GPs include: size of practice, location of practice, organization form, etc. Group level variables may be roughly classified into two categories:

1. Derived variables, such as mean age or percentage of females. In the literature, we find different names for these kinds of data which summarize distributions of individuals. Derived variables have been described by Diez Roux[11] as a type of group level variable which is constructed by mathematically summarizing the characteristics of the individuals in the group (i.e. means and proportions or measures of dispersion such as percentage of persons, mean income, and the standard deviation of the income distribution). Other names for derived variables are aggregate variables, compositional variables, and ecological variables. Some important derived variables are defined as combinations of more basic derived variables; an example is the neighbourhood social class measure, which is based on average mean and average education.
2. Purely contextual variables[26] that are directly defined. These variables are not summaries of the characteristics of individuals in the group. Dogan and

Rokkan used the term 'primary data'[27]. Examples of these purely contextual variables include: degree of urbanization (urban or rural), living in a socio-economically challenged versus non-challenged community, and type of practice (solo or group). Other names for this found in the literature are integral variables[11] and territorial variables[27].

We can describe the nesting of patients under GPs as a situation in which patients are seen as individuals and GPs are considered as collectives. The 'group' mentioned above then is defined, for a given GP, as the set of patients of this GP. Lazarsfeld and Menzel have made the distinction between individuals and collectives previously[28,29] and have identified four characteristics for individuals (i.e. patients) and three characteristics for collectives (i.e. GPs).

The four characteristics which apply to individuals are:

1. Absolute: an objective fact about the individual such as age.
2. Contextual: when a patient is described according to a characteristic which applies to a group of which the patient is a member (i.e. average age).
3. Comparative: when the patient is characterized according to a comparison with another patient (i.e. relative age, deviating from a mean age).
4. Relative: when the patient is characterized on the basis of his or her position in a network (i.e. number of contacts with other patients).

The three characteristics that apply to a collective are:

1. Analytical: when a characteristic results from a calculation involving patient characteristics (i.e. average age). In this case, average age is registered as a collective, and not as an individual characteristic.
2. Global: these are characteristics that are seen at the GP level. (i.e. location of practice and the GP's medical training).
3. Structural: when a characteristic is calculated based on a relationship pattern at the patient level. (i.e. size and number of families in a practice).

In terms of the distinction made above between derived and purely contextual variables, the first and third of the three types of characteristics of collectives may be regarded as a distinction between two types of derived variables, while the second type ('global') is the same as what was called above a purely contextual group variable.



In social science research, a number of investigators have been interested in the connections between individuals and the contextual settings of their lives[12]. This research method is known as contextual analysis and focuses on the effects of the social context on individual behavior[4,27]. It provides an important class of examples of multilevel studies. In health research (particularly in environmental health and epidemiology), the connections between individuals and their contextual settings are studied, looking, for example, at the relationship between a patient's health status and his or her geographical environment. The connections between individuals and their environments have been a notable focus in research which seeks to identify the role of factors in the external environment which influence individual susceptibility to disease[12]. The Jarman Index resulted from one such study[30]. The Jarman Index, described in 1984, is used to measure the demand for first line health care in specific regions. It can be used to identify regions where the demand for primary health care is higher than other regions. Reijneveld[31] did a study in which patients (at the micro level) were nested in geographical areas (the macro level). He examined the applicability of the Jarman Indices at the patient level in an urban GP setting in the Netherlands. There are many other studies in which connections between individuals and their contextual settings have been investigated[6,10,12,16,32-39]. Multilevel modelling was the statistical technique applied in these studies. Basic ideas of multilevel modelling are described and applied in this dissertation. A different but related technique is latent class analysis, which was used to study antibiotic prescribing in chapter 5, where a multilevel model was adapted to a longitudinal data structure. In this model, patients are the second level units who define the 'clusters' in the data. Whereas in the usual multilevel models individuals are assumed to differ by quantitative amounts, which show a normal distribution in the population, in latent class models it is assumed that these amounts have only a few possible discrete values showing an arbitrary discrete distribution across the values. Latent class analysis is much more flexible as it allows discrete classes which take the place of any standard distribution. This contrasts with standard multilevel models which assume a normal distribution.



### *2.2 The data structure seen in general practice databases*

Before developing a multilevel model, the hierarchy of the data structure must be explained. The lowest (i.e., most detailed) level measurements are considered to be at the micro level; all higher level measurements are said to be at the macro level[3].

For a general practice, we found that the most common data structure consists of individual units which fall into a number of clusters or groups[39]. The individual units are the patients, and the clusters may be the GPs or other clusters such as the neighbourhoods. For example, if we want to make inferences about patient prescriptions, adherence to guidelines, or GP workload in socio-economically challenged communities, it is useful to apply a multistage sampling study design in which the patients are selected via the GPs[4].

Figures 2.1 and 2.2 show examples of two level structures. Hierarchies may consist of more than two levels as is shown in figure 2.2. Patients who are registered with the same GP are more likely to receive similar care than patients registered with different GPs (see figure 2.1). Similarly, the GPs' treatment decisions may be influenced by their specific practice styles (for example, policies with respect to generic prescribing) which will again vary from practice to practice[19]. These are examples of the interesting dependency of microlevel unit (patient) observations on macrolevel (GPs) characteristics. In abstract terms, this dependency could result from:

1. Patients sharing the same physician;
2. Patients within a practice influencing each other by direct communication or shared group norms;
3. Patients within a practice living in the same community[4];
4. Patients within a group practice sharing the same GPs. This results in a three level design where patients are nested under GPs and the GPs in turn are nested under general practices.

**Figure 2.1**

**Patients (Pj) nested under the general practitioner(GPi); i = 1..k ; j = 1..(n, m, p, q)**

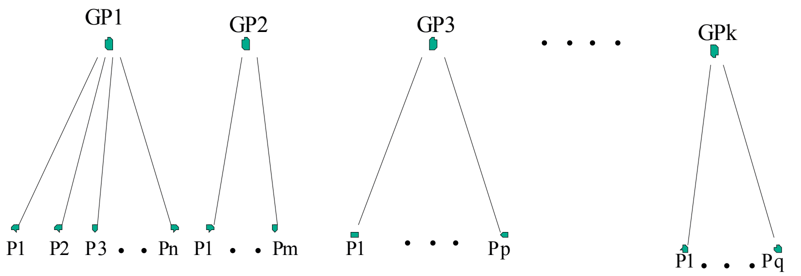
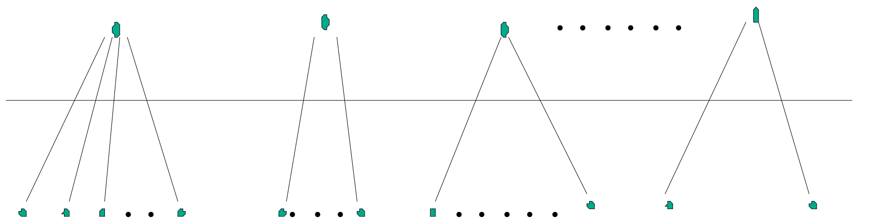



**Figure 2.2**

**Macro/micro distinction**

**MACRO – LEVEL (Level 2)**



**MICRO – LEVEL (Level 1)**



Such a hierarchical clustering structure imposes a correlation structure on the data which invalidates classical assumptions of independence and, therefore, common techniques such as ordinary least squares regression become inefficient or even misleading. Furthermore, a single level approach to the analysis of such hierarchically clustered data may fail to fully exploit the richness of information contained within and between the various levels being considered[19].

## *2.3 Choice of multilevel model*

*Use of multilevel model*

A level in multilevel analysis is a population within which there is meaningful variation that is reflected in the phenomenon under investigation. Thus, in a multilevel analysis there are always several populations involved. For example, in a study of the adherence to guidelines in a population of GPs, or variability among GPs with respect to workload or involvement in continuing education, there are a population of GPs as well as a population of patients involved.

There are three kinds of criteria for choosing levels and choosing numbers of levels for a given scientific investigation:

1. The theory under investigation[4,17] or the research question
2. The type of sample being used (i.e. multi-stage sampling)[4,17]
3. The number of units belonging to a particular level (e.g., when there are only three units at the highest level there is no point in including that level in the final analysis).

For a given study, it is not always clear at the outset how to define the levels and there are times when none of the above mentioned criteria can be used to determine the levels, as there is insufficient data to justify applying results to the population being studied. With respect to leaving a level out, several studies have concluded that the variation which would occur in the excluded level, is distributed over the remaining levels[40]. For example, if we take a three level model, in which patients (level 1, micro level) are nested under GPs (level 2), and GPs are nested within general practices (level 3, macro level), it would be possible to eliminate level 2 entirely. Moerbeek[41] showed that in a balanced situation, the variation occurring at the level of the GP moves in part to the general practice level and in part to the patient level. Both Moerbeek[41] and Hutchison[42] indicated that this shift of variation also occurs with an unbalanced design. Identifying one or more levels above the individual level is warranted when more than one population influences the dependent variable. If the social context (group level) affects the patients, there must be processes that depend on the characteristics of the social context (e.g., community). Groups or communities can have a direct effect on patients or there may exist cross level interaction effects which are defined as interactions between a patient level variable and a context variable. This requires the specification of processes within patients that cause those patients to be differentially influenced by specific aspects of the context.



In figure 2.1, the nesting structure of the patients (Pj) nested under GPs (GP1, ..., GPk) is shown. The number of patients for each GP may differ (shown in the figure as n, m, p, q respectively). In figure 2.2, a horizontal line between the two levels denotes the levels. Level 2 (macro level) is above the line and level 1 (micro level) is below the line. Level 2 represents the GPs and level 1 represents the patients. At the patient level, a single level regression equation is specified which may be estimated within each higher level (the GPs). In other words, just as with traditional regression, the researcher assumes that a common model is appropriate across all units at the second level. At this stage, the primary difference between ordinary regression and multilevel regression is that the researcher conceptualizes the overall data structure differently with multilevel techniques, acknowledging the existence of the higher level units under which the lower level units are nested[4,13,15,43], which will lead to a positive residual correlation between lower-level units within the same higher-level units.

There is a logical progressive sequence common to the development of all multilevel regression analyses, which we describe here for the case of patients nested under GPs.

1. The researcher analyzes variance in an outcome variable, paying special attention to the distribution of this variance within and between GPs[15].
2. Attention is paid to the development of a random intercept model, which is a regression model extended with random differences between GPs in the mean of the outcome variable[15].
3. The researcher conducts both theoretical and empirical investigations to discover for which of the patient variables the effect varies across GPs, the so-called random slopes[15].

4 Models are developed using higher level variables in an effort to explain variation between GPs in parameters discovered in previous stages[15].

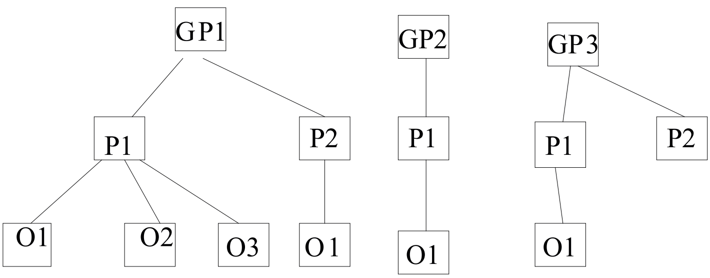
Multilevel models are useful and necessary only if the extent to which the data is being analyzed shows sufficient variation at each level. 'Sufficiency' of variation is relative and depends as much on theoretical and inferential concerns as on the structure and quality of the data[15]. Step 1 in developing a multilevel regression model serves to examine the extent to which variation in patient outcome exists within GPs relative to the variation between GPs. This is also known as the 'empty model'. The 'empty model' yields a number of important pieces of information. In the situation where level 1 units are patients nested under GPs (level 2 units):

1 The empty model yields an estimated mean score of the dependent variable for all GPs.
2 This model provides a partitioning of the total variation in scores between level 1 (patient) and level 2 (GP).
3 The empty model provides a measure of the dependence between the patients for a given GP through use of intraclass correlation.
4 A measure of the reliability of each GP's mean score is provided in case one wishes to use this mean as a measurement for a GP characteristic.
5 The model provides the means for a formal test of the hypothesis that there is no systematic variation between GPs on the outcome variable.



**Figure 2.3**

**A three-level model in which occasions (O.) are nested under patients (P.) and patients (P.) are nested under GPs (GP.) GP=general practitioner; P=Patient; O=Occasion**




The above remarks illustrate different ways of considering the relationship between the GP and the patient using a multilevel structure. The relationship between the GP and his or her organization may be looked at in a similar way, as this is also a nested data structure. Whether this is important for a given study will have to be addressed on a case by case basis as it is dependent on the research question being investigated.

When we expand a two level model to include repeated measurements for individual patients, we end up with a three level model. Figure 2.3 shows a symbolic representation of a three level model with the measurements (O.) nested under the patients (P.), and the patients nested under the GPs (GP.). In this thesis, we will limit ourselves to the following levels:

- A general practice where one or more GPs work cooperatively (general practice level),
- GPs who treat patients (GP level),
- Patients nested under GPs (patient level),
- Individual patients with multiple measurements (intra-patient level),

Each level in this structure has certain characteristics.
Based on the literature, the following four divisions of characteristics may be named:

- General practice linked characteristics (I)[44,45].

Some examples of general practice characteristics are: 1) the size of the practice; 2) the number of patients seen per day; 3) the distance to the nearest hospital; 4) the degree of urbanization; 5) the age and gender distribution of the practice population; 6) the role of the practice assistant; 7) the availability and use of the diagnostic and therapeutic aids

- GP characteristics (II)[44,45]

Examples include: 1) the age of the GP; 2) the number of years of experience as a GP; 3) involvement in continuing education activities; 4) having a pharmacy on site or not; 5) number of patients; 6) the GP's attitude; 7) type and scope of diagnostic facilities; 8) the distribution of the practice population according to age and gender; 9) length of contact time with patients

- Patient-linked characteristics (III)[44,45]

Examples include: 1) type and seriousness of medical condition; 2) patient's socio-economic status; 3) patient age; 4) patient gender; 5) patient ethnicity;

- Intra patient linked characteristics (IV)[45]

Examples include: 1) nature of complaint; 2) prescribed medication



### *2.4 Advantages of multilevel methodology*

The development of multilevel modelling allows new perspectives.
In multilevel research, the data structure in the population is hierarchical (e.g. patients nested in a general practice), and the sample data are viewed as multistage samples from the hierarchical population. In such samples, the individual observations (patient based) are generally not completely independent because of selection processes and because of the common context as a result of belonging to the same group (see Figure 2.1). Multilevel models take these dependencies into account[17].
When a researcher regards the groups as unique entities and tries primarily to draw conclusions pertaining to each of these specific groups individually, then it is appropriate not to use a multilevel analysis but rather an analysis of covariance. This analysis can estimate and test if differences exist between the groups, but cannot test the effects of group level variables which is necessary to study the antecedents or causes of such differences[3]. On the other hand, if a researcher wants to generalize to a population of groups (in our case: a population of GPs or practices), and possibly to investigate the effects of GP characteristics on patient outcome variables, a multilevel study is more appropriate.

Advantages when using multi level modeling techniques are the following.

1 With multilevel modeling, the different sources of variation are taken into account, in contrast with the more standard single level statistical methods, which have a single source of variation.
For example, when patients are nested under GPs, there are two sources of variation: the patients and the GPs. If the data would be aggregated to GP level or distributed to the patient level, we would only see one source of variation. It is necessary to take the hierarchical nature of the data structure into account and the multiple sources of variation, if we wish to have accurate the standard errors of estimates, type-I error rate of statistical tests, and reliabilities of measurement. In a multilevel model, the patient groups from each practice are seen as a random sample of a population of groups rather than as a random sample of individuals. One example may be seen in the study of guideline adherence (chapter 3). The hierarchical nature of the data structure here was taken into account. The sample took place in two stages. First the GPs were selected, and then all of their patients were included.



2 Multilevel analysis distinguishes between regression effects within and between the GPs. At the patient level (looking at GPs) we can ask the question of whether or not the gender of the patient has an effect on prescribing, and then we can do a comparison of different GPs to find out if the gender ratio in the practice has an effect on prescribing. The former is the within-GP regression of prescribing on gender; the second is the between-GP regression.

3 GPs may also be ranked according to their prescription behavior by making use of the so-called posterior means, while controlling for the composition of the patient population of each GP.

4 Another advantage is being able to look at differential effects. We can look at whether GPs prescribe differently when the patient belongs to a lower socio-economic class, and even if such differences vary when comparing GPs. The latter is reflected by the so-called random slopes in multilevel analysis.

5 Multilevel modeling gives us the chance to look at cross level interactions, which means that the interactions between patient characteristics and GP characteristics may be studied. For example, we could study if prescribing patterns that depend on socio-economic status also are related to the size of the practice.

6 Longitudinal data shows a special form of nesting. The dependence of the different measurements is important in a longitudinal data set, because the measurements are observed each time for the same patient.

7 The original data structures are retained in multilevel modeling; therefore, aggregation is not needed. A two level structure, e.g., with repeated measurements nested under patients, is the very minimum required.

8 All patients with missing data values may be included in the analysis, even though values are missing for one or more variables for these patients. This is due to the permitted format of the data structure. The data structure in use with repeated measurements, known under several terms such as univariate format[46], multiple record file[47], long data, and person period[46], is permitted to be unbalanced, i.e., have different numbers of observations for different patients.

9 Multilevel models require fewer assumptions than classical ANOVA-models and are less stringent in their application. However, a few key assumptions are still necessary for the estimation procedures used in multilevel models. The assumptions which are essential to a multilevel model are randomly distributed residuals. For classical ANOVA models, the compound symmetry characteristic and the assumption of sphericity are important, and these are stronger assumptions. Multilevel models require neither compound symmetry, nor sphericity, nor homoskedasticity.



10 The empty model (with no explanatory variables) is equivalent to a single level one way random effect ANOVA.

*Aggregation/disaggregation vs. multilevel analysis.*
The traditional approach to multilevel problems before the invention of hierarchical linear modelling was to aggregate the data to a super level (e.g., patients' medications are averaged to the general practice level and general practices are used as the unit of analysis) or to disaggregate data to the base level and ignore dependencies. An example of disaggregation is the following. For each patient, a number of variables are assigned at the practice level, such as type of practice (i.e. solo or group), which would cause all patients in a given practice to have the same value for this contextual variable. The patient would then be used as the unit of analysis. Ordinary regression or another traditional technique would then be performed on the chosen unit of analysis. There are three problems with the traditional approach: (1) Statistical power is lost as fewer units of analysis at the superlevel replace many units at the base level through aggregation; (2) disaggregation results in the misinterpretation of information from units at the superlevel, when it is erroneously treated as independent data for the many units at the base level. This error leads to overly liberal conclusions of significance; and (3) with both aggregation and disaggregation, there is the danger of *multilevel fallacies*: there is then no adequate analysis differentiating the individual level and group level relationships among the variables. With the *ecological fallacy*, a relationship found at the individual level between two variables is interpreted as a relationship at the group level. The *atomistic fallacy* is the ecological fallacy's counterpart. With the atomistic fallacy, a relationship found at the individual level between two variables is interpreted as a relationship at the group level. The atomistic fallacy is also known as the individualistic fallacy. Besides these two fallacies, there are an additional two fallacies which should be mentioned[48]:

1 The psychologistic fallacy: This occurs when relevant group variables are not taken into account when analyzing data and drawing conclusions at the level of the individual.

2 The sociological fallacy: The converse occurs in this fallacy, as individual variables are not taken into account when analyzing data and drawing conclusions at the group level.

Schematically, an overview of the four fallacies is presented in the following table:

| | | Level of inference | |
|---|---|---|---|
| | | Individual | Group |
| Unit of analysis | GP level | Ecological fallacy | Sociological fallacy |
| | Patient level | Psychologistic fallacy | Atomistic fallacy |

### *2.5 The research questions*

In this thesis, we will be concerned with variation in general practice and health care interventions. The general research question is: which patient and general practitioner characteristics are related to the prescribing of medication. In order to answer this general research question, a multilevel design will be used. Related to this question the methodological question is: what is the contribution of multilevel analysis to answer this question with data from registration databases. We will look at four areas having to do with prescribing and for which a case-mix adaptation will be applied. Case-mix[49] reflects the factors which characterize the patient population in terms of diagnosis, age, gender, etc., and using a case-mix adaptation aims to control the influence of these factors. The topics addressed in these four areas are:

1 The relationship between prescribing and adherence to guidelines.
2 The relationship between the GP's workload and the patient's socio-economic circumstances.
3 Describing antibiotic prescription behaviors, while at the same time taking into account the diagnosis variation.
4 Decreasing benzodiazepine prescriptions in an intervention study.



What the above four areas have in common is the variability in the general practice. Davis[50] uses the same premise as McPherson, which states that the effect of the different sources of variation in medical intervention depends on the aggregation level at which the data are analyzed. Davis[50] attempts to relate the sources of variation to the aggregation levels. The levels of aggregation which he identifies are: countries, regions, and GPs. With respect to the sources of variation he distinguishes: morbidity, population, health care system, professional, and unexplained.

With multilevel analysis we want to discover which contextual and compositional characteristics are related to inter and intra practitioner variation. In chapters three through six, we elaborate further on the general practice variation relevant to the four areas of study.

In the first study (chapter 3), applying concepts developed by Kamps[51], we looked at the extent to which GPs prescribe medications which are included in a set of guidelines. Kamps[51] identifies two types of compliance. Global compliance is said to exist when the medications listed in the guidelines are prescribed.

Specific compliance occurs when the medications are prescribed according to the diagnostic indicators listed in the guidelines. In this study, we look at how general practice and patient characteristics contribute to the global compliance with standard guidelines for prescribing.

In the second study (chapter 4), we look at patient, GP, and community characteristics to evaluate GP workload. This data is stratified according to type of health insurance coverage.

In the third study (chapter 5), using a longitudinal data set, we examine antibiotic prescribing patterns. Here, we try to find out how the variation in prescribing over time is structured at the patient level. Moreover, on an individual level, we looked at how this is related to demographic characteristics of the prescribing patterns of patients.

In the fourth study (chapter 6) variations in benzodiazepine prescriptions are investigated using an intervention study. The intervention is done at the GP level, but the dependent variable is at the patient level.

The data for all four of the studies comes from administrative databases, which are patient based. In all studies a multilevel study design is applied.

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*Chapter 3*

# *Factors influencing adherence to guidelines in general practice*



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## *Abstract*

*Objectives:*
To identify and assess the effects of physician and patient characteristics on global adherence to pharmacotherapeutical guidelines.

*Methods:*
In a cross sectional study in the northern Netherlands where a two level multilevel model was applied to patients (n = 269,067) in 190 practices with a total of 251 general practitioners, where the main outcome measures was the identification of significant indicators for good prescribing on patient and practice level.

*Results:*
The mean global adherence was 82%. Two general practice variables, organisation form and degree of urbanization influenced the global adherence, while all patients variables (age and gender) and the patient related prescription characteristics (costs, volume, different ATC-codes) were significant predictors for the global adherence. The total explained variance was 28%.

*Conclusions:*
Patient characteristics have a greater influence on prescribing behavior than physician characteristics.



*Keywords:*
Practice guidelines, Multilevel model, The Netherlands

### *3.1 Introduction*

In 1987, the World Health Organisation (WHO) published a statement about good prescribing: “rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time and at the lowest costs to the community”.[1] To amplify this statement, Barber described good prescribing as based on four criteria: maximize effectiveness, minimize risks, minimize costs, and respect for the patient’s choices.[2]
It is not easy for general practitioners (GPs) to comply with the above criteria, as the prescribing of drugs is a process affected by many factors.
Kamps et al. chose adherence to a set of regional pharmacotherapeutical guidelines as a criterion for good prescribing.[3] They evaluated the adherence of 16 GPs to the third edition of the Groningen formulary (GFIII)[4], taking into account two forms of adherence: global adherence, defined as the prescribing of a drug mentioned in the formulary; and specific adherence, defined as the prescribing of a drug mentioned in the formulary for an indication which is also mentioned in the formulary. The global adherence varied from 76-89% and the specific adherence from 55-71%. GPs with a high percentage of adherence were considered to be appropriate prescribers.
Factors which can act as predictors for good prescribing are divided into patient related and physician related. Straand et al. estimated the incidence of inappropriate prescribing for the elderly at 13.5%.[5] Using a multilevel analysis, Houghton concluded that patients aged over 65 years used more prescriptions, and therefore indirectly contributed to higher prescribing costs. Independent of age, women were given more prescriptions by their GPs than men.[6] Elderly people living in a nursing home received more prescriptions than those living at home. This was accompanied by an increase in prescription associated health care costs.[7]
With respect to the identified GP related factors, funded and training practices are associated with prescribing fewer and less expensive drugs.[6] The level of knowledge of Canadian physicians and the financial demographics of the practice (government funded versus fee –for service physicians) are GP related factors which contribute to the inappropriateness of prescribing behavior.[8] Variation in GP prescribing and the associated costs can partially be explained by the number of partners in the practice, the level of poverty in the practice population, and the preceptorship status of practice.[9]
A review of 62 studies by Buetow et al. revealed circumstantial evidence for inappropriate prescribing by GPs in the UK.[10] However, qualification and quantification of the apparent indicators was not possible, because of limitations of these studies.
The effect which feedback has on prescribing habits is variable [11-13]also when computers are used to provide information about drug prescribing and the associated costs.[11,14] Consensus or guidelines may enhance the quality of prescribing. GPs adhered to 61 % of prescribing advices in the national guidelines of the Dutch College of General Practitioners.[15]
In the present research, we studied the contribution of practice and patient characteristics on global adherence to pharmacotherapeutic guidelines as a measure of good prescribing in a general practice setting. Moreover, we assessed the interpractice variation.

## 3.2 Method

In the Netherlands, community pharmacists deliver medications as they are prescribed by the GP. The prescriptions for patients with obligatory public health insurance, approximately 60% of all patients, were registered. The data were collected over the period January to December 1997 in the province of Groningen in the North of The Netherlands. At that time the population of Groningen was 558,000 (3.6% of the Dutch population). The database included 269,000 patients with approximately 3.2 million prescriptions.

### 3.2.1 General practices

The following variables were recorded: the number of male and female patients; the gender and the mean age of the GP; the localization of the practice (rural if the population density is less than 1,500 addresses per square kilometer or urban if the population density of the environment is 1,500 addresses per square kilometer). The number of GPs per practice was also recorded, as well as the type of practice (solo practice and group practice). For each patient, age and gender were recorded. For each prescription, the Anatomical Therapeutic Classification-code (ATC), the Defined Daily Dose (DDD), and the costs were registered (in Euro). The number of different ATC's was considered as a proxy for multiple morbidity and severity of morbidity.An ATC was missing in 6% of the 3.2 million prescriptions.



Global adherence was defined as a prescribing of a drug which is mentioned in the Groningen Formulary (GFIII). The GFIII appeared for the first time in 1991, and was formulated based on a consensus reached by three GPs, two specialists and seven pharmacists.[4] The third edition of the Groningen Formulary, published in 1995, was used for the present study. It contained 186 health classifications and 251 medications. Two of the GPs participating in the present study also participated in the development of the GFIII. As the database was blinded, it was not possible to identify these two GPs.

The GFIII was distributed to all GPs in the region, free of charge, by the public health insurance organization.

## 3.3 Analysis

The total database included 251 GPs from 190 general practices. Since the database of 3.2 million prescriptions was too large to analyse, a stratified random sample of 12.5% of patients per general practice was used. The data were analysed on a per practice basis, because public health insurance registration is not always GP based. All the prescriptions for each patient in the sample were included, and aggregated to patient-level.

The influence of the different factors and the interpractice variation were analysed with multilevel models. The dependent variable was the percentage global adherence per patient. The multilevel modelling technique from the SAS statistical package (Proc Mixed) and Mlwin program from Goldstein was used to analyse the data.[16,17]

Three blocks of variables were used in succession: practice related, patient related and to patient level aggregated prescription related variables. We used a two level model: level one the patient level, and level two the practice level. To obtain a meaningful interpretation of the estimated parameters, the data were centered on their grand mean.. The practice characteristics, type and localisation, and the patient characteristic gender are dummy variables (with values 0 or 1). The value 1 is for urban, solo practice and male patient respectively.

The following statistics were used:

1 Intraclass correlation coefficient (ICC). It measures the proportion of the variance which exists in the global adherence between different practices. [18,19]
2 Explained variance
3 -Log-likelihood, which is useful for comparing the goodness of fit of different models. If the ratio between parameter estimate and standard error is larger then 1.96, then the parameter estimate under consideration is significant.

Several models were used in succession. First, the baseline (or null) model concerning the influence of the variation on global adherence was fitted. With the addition of other variables (three blocks), the influence of practice characteristics (Model A), patient characteristics (Model B) and patient related prescription characteristics (Model C) was assessed. In Model D, only the significant variables were indicated.



To investigate if interdependent relations existed between different variables, interactions between two variables were studied. In model D a cross level interaction between two variables of different levels was studied: age of the patient and morbidity.

In the models described above, the so-called fixed effects were described. The objective of fixed effects is to compare means of treatment groups or populations, while random effects are computed when the objective is to determine sources of variability. The latter were studied to assess which patient characteristics are responsible for the interpractice variation (model E). In order to determine which variables are the most important, the coefficients of the final model will be standardised.

### *3.4 Results*

The mean age of practitioners per practice was 48.2 years (SD 6.0). Of the general practitioners 91% were men (SD 24.2). The number of solo practices was 149 (78.4%), while 30 (15.8%) were duo-practices and the remaining 11 (5.8%) were group practices with three to six GPs. 60% of the practices were situated in an urban area.

The mean number of male patients per practice was 681.8 (SD 209.3); and the mean for female patients was 749.2 (SD 208.1).

Table 3.1 shows that the sample was found to be a good representation of the total database with regard to the patient characteristics age and gender, the prescription characteristics costs, DDD and number of different prescriptions per patient and the global adherence.

Table 3.2 shows the different models that were assessed.

**Table 3.1**

**Patient characteristics in database and sample**

| | Total database | Sample |
|---|---|---|
| **Patient characteristics** | | |
| Number | 269067 | 33432 |
| Mean Age | 42.92 (22.97) | 43.00 (22.83) |
| Male (percentage) | 41.9% | 42.0% |
| | | |
| Precription characteristics | | 405045 |
| Number | 3244684 | 45.21 (110.15) 405045 |
| Mean Costs (FL) | 45.43 (126.37) | 37.47 (50.8) |
| Mean Volume (DDD) | 37.82 (51.04) | 37.22 (38.44) |
| Mean of different prescriptions | 4.24 (3.90) | 4.34 (3.88) |
| Percentage global adherence * | 0.79 (0.41) | 0.79 (0.41) |

Mean and between brackets standard deviation; *(computed on prescription level)



In Model 0 the maximum likelihood estimate for the global adherence is 82% (standard error 0.33). The maximum likelihood estimate of the variance component at patient level was 682.9 (standard error 5.3) and the estimated variability of means for the different practices was 15.4 (standard error 2.1). These variance components indicate that most of the variation of the global adherence was not at practice level, but at patient level. The intraclass correlation (ICC) of 0.02, indicated that 2% of the variance in global adherence existed between practices.
In Model A, in which the practice characteristics were added, the mean global adherence (82%) did not change. The variables organisation form and urbanisation degree were the only significant practice characteristics revealed with model A. The interaction term (organisation form by urbanisation degree) was not significant. In table 3.2 Model 0 yields a deviance of 308,373.6, while Model A has a deviance of 308,345.7. The difference 27.9 is significant as calculated with a chi-squared distribution test with seven degrees of freedom (d.f.).
In Model B, patient characteristics were added, and the level of adherence stayed the same (82%). The age and gender of the patient were both significant factors, and their interaction term, age by gender, was also significant. The deviance difference between Model 0 and Model B was 536.2. This difference is significant when calculated with a chi-squared distribution test having three degrees of freedom.
In Model C, the patient related prescription characteristics (as aggregated prescription to patient level) were added. All of these characteristics (costs, volume and different ATC-codes) were significant. In this model, the cross-level interaction term between age of the patient and different ATC-codes was also significant. The deviance difference between Model 0 and Model C is 1,175.2 (is significant in a chi-squared distribution with four d.f.).

**Table 3.2**

**Parameter estimates for five multilevel models (and standard errors)**

| | Model 0 | Model A | Model B | Model C | Model D |
|---|---|---|---|---|---|
| Intercept | 82.44(.33) | 82.44 (.31) | 82.57 (.33) | 81.98 (.31) | 82.03 (.29) |
| **GPP characteristics:** | | | | | |
| Mean age | | -.045 (.052) | | | |
| Perc. male GP | | -.022 (.014) | | | |
| Mean male patient | | .010 (.007) | | | |
| Mean female patient | | -.011 (.007) | | | |
| Type of practice (ref: solo) | | -1.97 (.85) | | | |
| Localisation of the practice | | | | | |
| (ref: urban) | | -1.75 (.72) | | | -2.36 (.69) |
| | | | | | |
| Interaction-term | | | | | -1.99 (.60) |
| Type of practice * | | -.13 (1.67) | | | |
| localisation of the practice | | | | | |
| Patient-characteristics: | | | | | |
| Age | | | -.13 (.0064) | | -.087 (.0069) |
| Gender (male) | | | -2.997 (.29) | | -1.79 (.2997) |
| | | | | | |
| **Interaction-term** | | | | | |
| Age and Gender | | | .098 (.013) | | .068 (.013) |
| Aggregated patient features | | | | | |
| Mean costs(Euro) | | | | -.062 (.0029) | -.12 (.0064) |
| Mean volume (DDD) | | | | .087 (.0038) | .081 (.004) |
| Different ATC | | | | -.72 (.044) | -.57 (.047) |
| | | | | | |
| **Cross-level** | | | | | |
| Interaction-term | | | | | |
| Age and different ATC | | | | .012 (.0017) | .013 (.0017) |
| Variance | | | | | |
| Level 1 Patient | 682.94 (5.34) | 682.94 (5.34) | 672.05 (5.26) | 659.34 (5.16) | 654.82 (5.12) |
| Level 2 GPP | 15.42 (2.05) | 12.69 (1.77) | 14.42 (1.94) | 13.11 (1.8) | 11.13 (1.58) |
| ICC | 2% | 2% | 2% | 2% | 2% |
| Explained variance Level 1 | ------ | 0% | 2% | 3% | 4% |
| Explained variance Level 2 | ------ | 18% | 6% | 15% | 28% |
| -2 Log Likelihood | 308373.60 | 308345.7 | 307837.4 | 307198.4 | 306950.2 |

**Figure 3.1**

**Relation between global adherence (percentage) and age of the patient, including the contraceptive pill-ATC-codes**

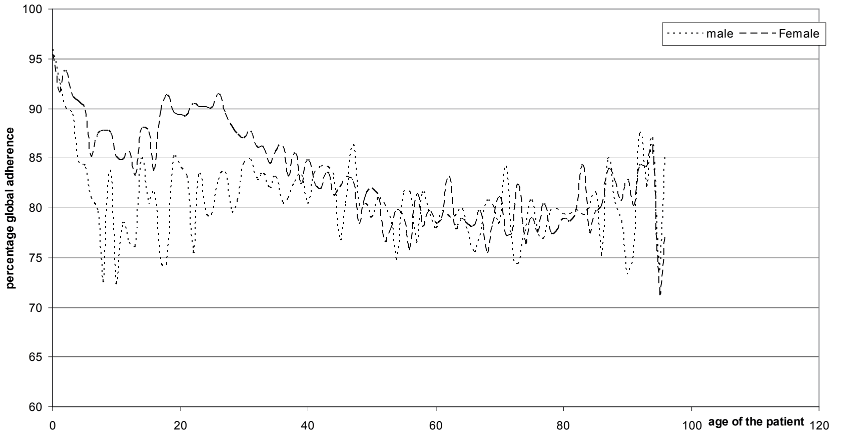
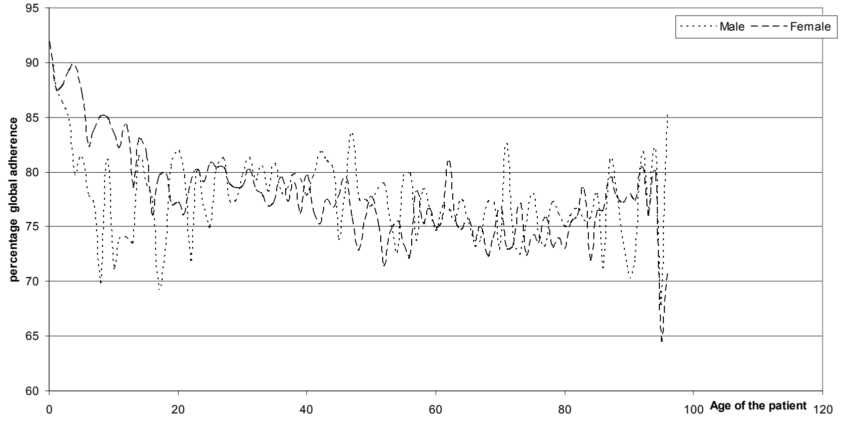



**Figure 3.2**

**Relation between global adherence (percentage) and age of the patient, excluding the contraceptive pill-ATC-codes**




In figure 3.1 the relation between global adherence and age for men and women is illustrated. An important difference between the genders became apparent, particularly in the age group 15-35 years. We assumed that the effect was mainly due to the contraceptive pill, since the prescription of nearly all the contraceptive pills is adherent to the formulary.
Figure 3.2 shows that the difference in gender for all ATCs without inclusion of the contraceptive pill codes (G03AA, G03AB, G03FA, G03FB and G03HB) virtually disappeared in the age group 15-35 years. This clearly illustrates the effect of the contraceptive pill.

**Table 3.3**

**Parameter estimates of the random-coefficient model of the significant variables (and standard errors)**

| | Model E | |
|---|---|---|
| | **Fixed effect** | **Random effect** |
| Intercept | 82.00 (.29) | |
| | | |
| **Practice characteristics** | | |
| Organisation form (ref:solo) | -2.31 (.69) | |
| Urbanization degree (ref: urban) | -1.72 (.600) | |
| | | |
| **Patient characteristics** | | |
| Age | -.081 (.0079) | .023 (.0010) |
| Gender (ref: male) | -1.4 (.34) | 4.11 (1.97) |
| | | |
| Interaction-term | | |
| Age by Gender | .066 (.013) | .0 (.0) |
| | | |
| **Aggregated patient characteristics** | | |
| Mean costs (Euro) | -.19 (.012) | .010 (.0023) |
| Mean volume (DDD) | .0898 (.0041) | .0 (.0) |
| Different ATC | -.53 (.047) | .0 (.0) |
| | | |
| Interaction-term | | |
| Age by different ATC | .012 (.0017) | .0 (.0) |
| | | |
| **Variance** | | |
| Level 1 Patient | 647.64 (5.10) | |
| Level 2 Practice | 11.15 (1.593) | |
| ICC | 0.0169 | |
| Explained variance | 28% | |
| -2 Log Likelihood | 306799.1 | |



*Model D*

The total explained variance for all significant factors that influence global adherence was 28%. These are as well practice as patient related, and constitute the fixed effects in model E.

*Model E*

The interpractice variation is studied using the random effects seen in Model E (Table 3.3). The effects which differ between practices were the age and gender of patients and mean prescription costs. The most important variable is the age of the patient, followed by the cost, the mean volume (DDD), different ATCs, the interaction between age and different ATCs, organisation form and finally urbanization degree , gender and age by gender.

### *3.5 Discussion*

The present research shows that two of the general practice characteristics and all the patients' characteristics influenced the degree of adherence to guidelines.
The study does have limitations, however. Firstly, the population included only patients (ca. 60%) having obligatory health insurance. Secondly, only the adherence to advised medications could be studied, as the database used did not contain indications for prescriptions. We assume that studies adding prescription indications might result in superior models.[3,10,20] In all the models studied, a global adherence of 82% was found, which is comparable to the results of others (Kamps, Barber and Grant).[2,3,21] 28% explained variance was due to the characteristics of the general practices and patients. The differences between patients are much greater. Other variables which may account for the remaining unexplained variance are hospital initiated prescribing, the prescription history of the patient and patient insistence. [20] Therefore the development of models which take the patient's perspective into account is necessary.



Compaired to the study of Davies and Gribben, in which the practice variable small practice was one of the significant predictors we found a significant contribution of our organization form. [22]
All the patient characteristics affect global adherence, including the interaction age by gender and the cross-level interaction age by different ATC. Since there was a negative relation between the age of the patient and the global adherence, The GP appeared generally less compliant with guidelines as the age of the patient increased. Multiple morbidity in the elderly likely is a contributing factor for this trend. In a patient with multiple morbidity, GPs more often prescribe medications of second choice. This explanation also applies to the negative relation which exists between global adherence and the number of different ATCs. Usually, a patient who is more seriously ill or who suffers from multiple diseases is prescribed more medications, including an increasing number of second choice medications, which are not mentioned in the formulary.
The total number of prescriptions in a practice correlates positively with global adherence. This could be caused by the increased number of repeat prescriptions.[23] As the cost increased, adherence decreased. This is in agreement with one of Barber's criteria, as increasing adherence would therefore tend to minimise costs.[2] The negative relation between global adherence and cost for the fixed effects implies that, in general, when global adherence increases, mean cost decreases. The random effect of mean cost indicates that the general practices show different relations between global adherence and mean cost. All these significant characteristics of patient and practice merit further investigation to improve the quality of prescribing in general practice.

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# The workload of general practitioners in disadvantaged urban communities



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***Abstract***

In 1996, a fund was set up by the Ministry of Health and health insurance companies in order to give financial support to general practitioners (GPs) who have patients living in disadvantaged communities. The relationship between patients and their GP may be modelled in a hierarchical, nested structure, as well as the relationship between patients and where they live (postal code region). The model which is used here is a cross-classified multilevel model. With this model, the workload will be evaluated with data from the morbidity Registration Network Groningen (seven GPs) and data from the biggest regional health insurance company (70 GPs). The data are stratified according to the way patients are insured. The workload of GPs is higher in disadvantaged communities. The most important determinants of the workload are patient characteristics such as age and gender. The characteristics of the GP are of minor importance. According to this study, the number of foreigners in a particular community appears to have no clear influence on the workload. The method of calculating workload may be improved by assigning greater importance to the patient factors. Replication research is necessary to determine if the results are also applicable to other cities with disadvantaged communities.



*Key words:*
Workload, general practitioner, disadvantaged communities, multilevel analytical techniques

## *4.1 Introduction*

Since the beginning of the 1990s there were increasing reports from general practitioners (GPs) concerning their large workload in disadvantaged communities in large urban centers[1]. This is still a relevant issue[2-10]. According to the Netherland's Institute for Health Services Research (NIVEL), a disadvantaged community is characterized by inhabitants with a low socio-economic status and complicated health issues. To address this problem, in 1996 the Ministry of Health Wellness and Sports (VWS) and the health insurance companies set up a fund (Achterstands Ondersteunings Fonds AOF) to support GPs with patients living in such communities. Similar measures have been taken in the United Kingdom (UK) where funds were earmarked to compensate physicians for the higher workload resulting from caring for patients in disadvantaged communities[11,12]. In The Netherlands, communities were classified as disadvantaged according to the postal codes. Three criteria were used: (i) population density: the number of addresses in a specific postal code region quantified per square meter; (ii) the average income per working adult; and (iii) the percentage of people between the ages of 15 and 64 within the community who were receiving disability compensation. According to this method, a set of eight postal code areas were identified in 1996 in Groningen as disadvantaged. In the present article we address the following question: does the care for patients in disadvantaged communities require extra effort from the GP as compared with other communities? In answering this question, we will take into account the patients' demographic characteristics, their place of residence, as well as the way the GP's practice is organized.



## *4.2 Materials and Methods*

Seven GPs from Groningen participated in this study, all of whom were registered with the morbidity and medication Registration Network in Groningen (RNG) and affiliated with the Department of General Practice medicine at the University of Groningen (RUG). Four of these GPs work part-time as members of a group practice, and the other three are full-time solo practitioners. The data which were used for this article were prospectively collected during 1997[13].

The GP's workload is calculated taking into account the following variables:

1 The number of contacts with the patient.
2 The number of care episodes per patient, coded according to the International Classification of Primary Care (ICPC)[14].
3 The number of prescriptions per patient. The medications are automatically coded according to the Anatomical Therapeutical Classification system (ATC)[15].

In addition to the data obtained from the RNG, we also obtained the prescribing data of the 70 GPs in Groningen for patients registered with the largest health insurance company in Groningen (Geové-RZG) for 1997.

The disadvantaged areas were identified according to the criteria mentioned in the introduction which resulted in the identification of eight postal code regions (9711, 9713, 9715, 9716, 9724, 9729, 9741, and 9742)[16,17]. The percentage of foreigners living in each of these regions was calculated using information from the Statistics Netherlands (CBS) for 1997. A person is classified as an foreigner if s/he or at least one of the parents was born outside of The Netherlands[18].

### *4.3 Analysis*

To discover to what extent community, GP, and patient characteristics contribute to the GP's workload, the information of all the patients registered with the RNG in 1997 was linked with information on the communities as compiled by the CBS. The patients were registered with a GP and lived in regions designated by postal code. GP and postal code region factors were used during the analysis of the data. Using multilevel analysis techniques, variables from different hierarchical levels can be considered within a single model which takes into account the hierarchical nature of the information which is being analyzed[19-21]. Age and gender were used as characteristics at the patient level, whereas socio-economic status (disadvantaged or non-disadvantaged) and foreigner versus indigenous was considered at the level of the postal code region. At the GP level, we considered the type of practice (solo or group). The advantage of such a model is that the effects of community and practice organization are corrected for the demographic differences. This is achieved by using a cross-classified multilevel model[19-21].



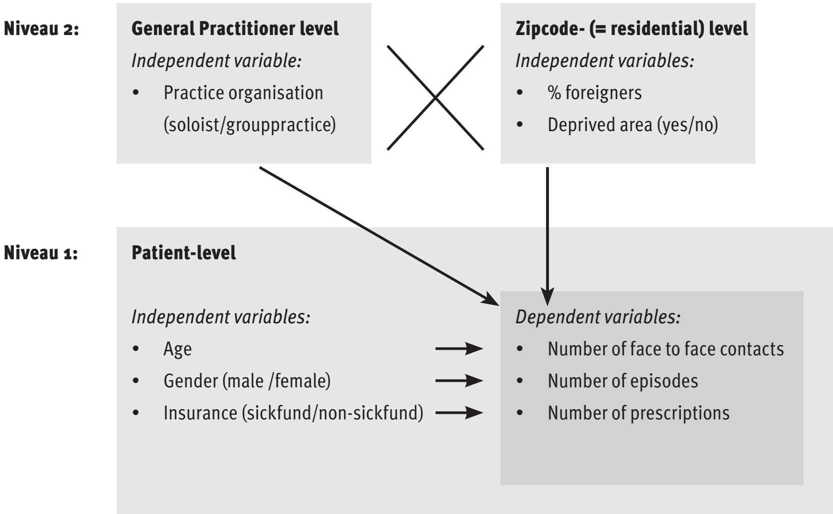
Figure 4.1 shows how the three levels of the model relate to the specific variables belonging to each level. The patients on the first level are clustered both under the GP and under their postal code region on the second level. The dependent variables can be found at the patient level. The arrows in figure one show the influence of the independent variables on the dependent variables. The binary variables practice organization (solo/group), gender (male/female), and socio-economic group (disadvantaged/non-disadvantaged) had, as their reference group: group practice, male, and non-disadvantaged respectively.

With the multilevel analysis, for the work load variable, a log transformation was applied, as these variables were skewly distributed. Figure 4.2 shows that the relationship between age and the natural log (ln) of the average number of prescriptions, divided according to gender, is non-linear. For all of the workload variables, a model was used which incorporated both age and age squared (second degree polynomial). We also looked at whether patients aged older than 65 added even more to the GPs workload.

With the analysis, the data were stratified according to type of insurance. The coefficients presented may also be interpreted from a regression model, for which the log transformation of the dependent variable has to be taken into account. By taking the antilog of the coefficient, the relative effect of the variable concerned is calculated. Regression coefficients between the strata were tested with a t-test[22]. A

Figure 4.1

**Cross-classified model**






confidence level of 0.05 was used. The significance of the variables was calculated using the standard deviation (s.d.). The variables age and percentage of foreigners were centered. This means that the average result is subtracted from each score. Variance components which are represented at the patient, GP, and postal code level show the amount of unexplained variance which is present at each level. As a log transformation was used, the variance maybe approximated as the square of the variation coefficient of the original variable. In the model presented here, patient, postal code region, and one GP variable were considered.

Because the RNG only contains the data for seven GPs, the model would be tested with the addition of the prescription data obtained from the Geové-RZG. The data from the Geové-RZG include prescription information for 66,028 patients with public health insurance registered with 70 GPs who practice in Groningen.

### *4.4 Results*

14,984 patients were registered with the seven RNG GPs in 1997 in the city of Groningen (Table 4.1). 5,906 of these (39.4%) lived in disadvantaged communities. Table 4.2 shows the demographics of disadvantaged communities versus other communities. There was no relevant difference in the male/female ratio with the disadvantaged communities being 53.3% female versus 52.7% female in other communities. The average age of residents living in disadvantaged communities was 37.8 years, whereas the average age of people living in non-disadvantaged communities was 35.1 years.

**Table 4.1**

**Characteristics of patients, GPs and zip code area, their means (standard deviation) or percentages**

| | |
|---|---|
| **RNG** | |
| Patients N = 14984 | |
| Mean age | 36.1 (20.7) |
| Gender (% women) | 53.0 |
| Insurance type (% sick fund) | 54.2 |
| Mean of face to face contacts | 1.9 (2.9) |
| Mean of episodes | 2.0 (2.6) |
| Mean prescriptions | 10.2 (23.1) |
| **GPs N = 7** | |
| Organisation of the practice (% soloist) | 42.9 |
| Mean of enrolled patients | 2142.6 (1053.4) |
| **Geové-RZG** | |
| Patients N = 66028 | |
| Mean age | 43.3 (22.3) |
| Gender (% female) | 61.1 |
| Mean number of prescriptions | 11.4 (17.5) |
| Insurance type (% sick fund) | 100.0 |
| **GPs N = 70** | |
| Organisation of the practice (% soloist) | 48.6 |
| Mean number of sick fund patients | 943.3 (337.5) |
| **RNG and Geové-RZG** | |
| Zip code areas N = 29 | |
| Social economic status (% deprived areas) | 27.6 |
| Mean percentage of foreigners | 13.2 (5.5) |



The average number of patients per RNG GP was 2,143 (sd=1053) (Table 4.1). 21.7% of registered patients did not have any contact with their GP in a single year (not included in Table 4.1). 54.2% of patients in the RNG had public health insurance (Table 4.1). Table 4.2 shows that the variables affecting GP workload were different for men and women from disadvantaged communities versus non-disadvantaged communities. This held true for the number of GP-patient contacts, the number of registered care episodes, and for the number of prescriptions. The number of GP-patient contacts was 23.9% higher in disadvantaged communities, the number of registered care episodes was 22% higher, and the number of prescriptions was 48% higher than in non-disadvantaged communities. These differences in workload could, in part, be caused by age differences among the communities.

According to the Geové-RZG database 36.4% of registered patients live in disadvantaged communities. On average, 943 publicly insured patients were registered per GP (sd=337.5) (Table 4.1). Prescriptions were 16.4% higher in disadvantaged communities (Table 4.2). The average patient age with public

**Table 4.2**

**Comparison between deprived areas (Deprived) en non-deprived areas (non-deprived) of the workload variables and age by RNG and the insurance company Geové-RZG, total en gender (mean standard deviation)**

| | | | Gender | | | |
|---|---|---|---|---|---|---|
| | Total | | Men | | Women | |
| RNG: | Deprived | Non-deprived | Deprived | Non-deprived | Deprived | Non-deprived |
| Face to face contact | 2.18 (3.3) | 1.76 (2.6) | 1.75 (3.1) | 1.41 (2.3) | 2.56 (3.4) | 2.06 (2.8) |
| Number of registered episodes (ICPC)* | 2.27 (2.9) | 1.86 (2.4) | 1.68 (2.3) | 1.39 (2.0) | 2.79 (3.3) | 2.28 (2.6) |
| Number of prescriptions | 12.67 (27.8) | 8.56 (19.2) | 8.43 (20.5) | 6.25 (16.8) | 16.38 (32.5) | 10.64 (20.8) |
| Age | 37.75 (21.4) | 35.08 (20.2) | 35.89 (19.8) | 34.10 (19.3) | 39.39 (22.6) | 35.95 (20.9) |
| Number of persons | 5906 | 9078 | 2756 | 4293 | 3150 | 4785 |
| Geové-RZG: | | | | | | |
| Number of prescriptions | 12.47 (19.6) | 10.71 (16.1) | 10.85 (20.9) | 9.48 (15.1) | 13.52 (18.7) | 11.49 (16.6) |
| Age | 44.99 (22.7) | 42.38 (22.0) | 43.13 (22.0) | 41.19 (21.9) | 46.05 (23.2) | 43.36 (22.0) |
| Number of persons | 24042 | 41986 | 9510 | 16203 | 14532 | 25783 |

* ICPC = International Classification of Primary Care



health insurance in disadvantaged communities was 45 years, whereas in other communities the average age was 42.4 years. This is a significant difference. ($p<0.05$)

The results of the multilevel analysis are presented in tables 4.3 and 4.4. To use the coefficients listed in tables 4.3 and 4.4, they first have to be divided by 1000.

When we look at the relationship between the number of patient-GP contacts (Table 4.3) and patient characteristics, gender and age are contributing factors for patients covered by public health insurance as well as for patients with private insurance. For patients with private health insurance, the effect of age is different for men and women. Patients with public health insurance in disadvantaged communities visited their GPs more often than those living in non-disadvantaged communities, after correction for all other variables. This difference was not seen for patients with private health insurance. The way the GP practice was organized did not influence the number of patient contacts. The number of care episodes, as is seen in table 4.3, was related to the way the practice was organized and to patients with public health insurance's residency in a disadvantaged community. Patients with public health insurance had 23% fewer episodes of care when they were registered with a GP working in a solo-practice (because exp(-0.255) = 0.77). The number of care episodes in disadvantaged communities was 9% higher for patients with public health insurance. The number of patient-GP contacts in disadvantaged communities was also 9% higher for patients with public health insurance.

The number of prescriptions written for women with private health insurance was 52% higher than for men, whereas for women with public health insurance the number of prescriptions was 73% higher than for men. Patients with public health insurance who lived in disadvantaged communities contributed more to the GP workload than those who lived in non-disadvantaged communities. In terms of prescriptions, the workload is 11% higher, after correction for all other variables. All the patient characteristics (age and gender) and the characteristics of the community (residency in a disadvantaged community and the percentage of foreigners) of the patients with public health insurance from the Geové-RZG database (Table 4.4) shows a relationship with the number of prescriptions, whereas no relationship was identified with the GP practice organization. Patients with public health insurance who lived in a disadvantaged community cause 7% more workload than publicly insured patients who live in non-disadvantaged communities. In the comparison of the three variation components, most of the variance, interestingly, is seen at the patient level. The variation coefficient for the number of prescriptions from the Geové-RZG data for the GP is 11% (=100% x √0.013). For patients, this calculation yields only a rough estimate.



The results in the previous sections were presented according to outcome variable. If we look at the results per determinant (tables 4.3 and 4.4), after correcting for other variables, the following becomes clear:

Gender and age are related to all aspects of work load for both patients with public health insurance as well as patients who are privately insured. The difference between men and women is greater for those who have public health insurance which is represented by the higher coefficients in table 4.3. For the three workload variables (patient contacts, number of registered care episodes, number of prescriptions) the workload (men less than women) for privately insured versus publicly insured patients is 18% versus 24%, 22% versus 30%, and 52% versus 73% respectively. The effect of age is different for women than for men when privately insured with respect to patient-GP contacts and the number of care episodes. The older the privately insured female patient, the greater the difference in the number of contacts and care episodes between men and women. The number of prescriptions, on the other hand, becomes less different from the men as age increases.
With respect to the effect of environment, we found that publicly insured patients who live in disadvantaged communities cause 7-11% more workload than publicly insured patients who live in non-disadvantaged communities. This difference is not seen for patients with private health insurance. When there is a higher percentage of foreigners in a particular community, we found that privately

**Table 4.3**

**Regression coefficients en standard error (s.e.) of number of face to face contacts en episodes of the RNG-data (multilevel regression) stratified by private insurance patients (ZF0) and public insurance patients (ZF1)**

| RNG-data | | Number of face to face contacts | | | | Number of episodes | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Model ZF0 | | Model ZF1 | | Model ZF0 | | Model ZF1 | |
| | | coefficient (x 1000) | s.e. (x 1000) | coefficient (x 1000) | s.e. (x 1000) | coefficient (x 1000) | s.e. (x 1000) | coefficient (x 1000) | s.e. (x 1000) |
| **Levels** | Variables | | | | | | | | |
| **GP** | | | | | | | | | |
| | Organisation: soloist | -5 | 56 | -99 | 53 | -112 | 101 | -255 * | 60 |
| **Neighbourhood** | | | | | | | | | |
| | Deprived area | -1 | 29 | 88 * | 27 | -1 | 30 | 89 * | 26 |
| | % foreigners | -8.1 * | 3.5 | 2.0 | 3.2 | -10.0 * | 3.6 | 0.0 | 3.1 |
| **Patient** | | | | | | | | | |
| | Age (yr) | 7.7 * | 0.8 | 6.8 * | 0.8 | 7.3 * | 0.8 | 6.7 * | 0.7 |
| | Age-square | 0.21 * | 0.03 | 0.07 * | 0.03 | 0.14 * | 0.03 | 0.00 | 0.02 |
| | Over 65 years | -1.8 | 0.9 | -0.3 | 0.8 | -0.3 | 0.9 | 2.3 * | 0.7 |
| | Gender: women | 166 * | 17 | 219 * | 17 | 196 * | 16 | 266 * | 16 |
| | Interaction : | | | | | | | | |
| | age and gender | 1.7 * | 0.9 | 0.7 | 0.8 | 2.1 * | 0.8 | 0.9 | 0.7 |
| **Variance #** | | | | | | | | | |
| | GP | 0.005 | | 0.005 | | 0.015 | | 0.006 | |
| | Neighbourhood | 0.002 | | 0.002 | | 0.003 | | 0.002 | |
| | Patient | 0.448 | | 0.527 | | 0.428 | | 0.467 | |

* $p < 0.05$; # variances are NOT multiplied by 1000;

**Table 4.4**

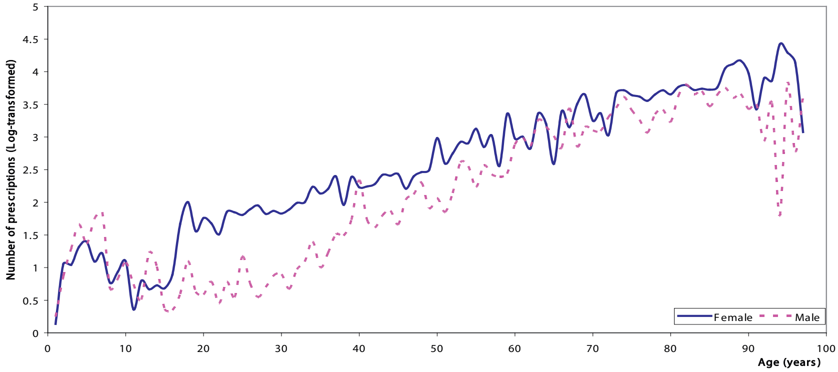
**Regression coefficients en standard error (s.e.) of the number prescriptions of RNG-data and Geové-RZG-data stratified by private insurance patients (ZF0) and public insurance patients (ZF1)**

| | | RNG-data: Number of prescriptions | | | | Geové-RZG-data: Number of prescriptions | |
|---|---|---|---|---|---|---|---|
| | | Model ZF0 | | Model ZF1 | | Model ZF1 | |
| | | coefficient (x 1000) | s.e. (x 1000) | coefficient (x 1000) | s.e. (x 1000) | coefficient (x 1000) | s.e. (x 1000) |
| **Levels** | Variables | | | | | | |
| **GP** | | | | | | | |
| | Organisation: soloist | -235 * | 110 | -480 * | 90 | -35 | 29 |
| **Neighbourhood** | | | | | | | |
| | Deprived area | -46 | 54 | 106 * | 52 | 65 * | 19 |
| | % foreigners | -3.6 | 6.1 | 3.7 | 5.8 | 9.7 * | 2.0 |
| **Patient** | | | | | | | |
| | Age (yr) | 18.6 * | 1.2 | 26.3 * | 1.2 | 26.3 * | 0.4 |
| | Age-square | 0.25 * | 0.04 | 0.13 * | 0.04 | 0.19 * | 0.01 |
| | Over 65 years | 4.2 * | 1.4 | 1.8 | 1.2 | -0.8 * | 0.3 |
| | Gender: women | 421 * | 25 | 551 * | 26 | 238 * | 7.9 |
| | Interaction : | | | | | | |
| | Age and gender | -0.3 | 1.3 | -2.9 * | 1.2 | -0.7 | 0.4 |
| **Variance #** | | | | | | | |
| | GP | 0.020 | | 0.014 | | 0.013 | |
| | Neighbourhood | 0.010 | | 0.010 | | 0.001 | |
| | Patient | 0.996 | | 1.276 | | 0.987 | |

* p < 0.05; # variances are NOT multiplied by 1000

**Figuur 4.2**

**The relation between the natural logaritm of the mean prescriptions and age for women and men of the RNG-data**






insured patients had fewer GP contacts and fewer care episodes than when the percentage of foreigners was lower. In the Geové-RZG database for publicly insured patients the number of prescriptions in a community was higher when there was a higher percentage of foreigners.

GPs who work in a solo practice write fewer prescriptions than those in a group practice. This is true for publicly insured patients (38% lower) and for privately insured patients (21% lower). Solo GPs registered 23% fewer care episodes than GPs in the RNG group practices.

In disadvantaged communities, all of the workload indicator coefficients differed depending on whether the patient was publicly or privately insured (tables 4.3 and 4.4). Namely, for: a) the number of GP contacts ($t=2.25$, $p=0.02$), b) the number of care episodes ($t=2.26$, $p = 0.02$), and c) the number of prescriptions ($t=2.04$, $p=0.02$)[22].

In tables 4.5 and 4.6 the effects of the patient's residence and GP characteristics are compared. The standardized coefficients allow us to compare the different variables according to the degree of impact each has. It turns out that age and gender contribute the most with respect to all of the workload variables.

## 4.5 Discussion

In this study, the workload faced by GPs in disadvantaged communities was examined using three separate, dependent variables (patient-GP contacts, care episodes, and prescriptions). These three variables all had higher values in these neighborhoods. The differences seen between disadvantaged communities and other communities, for patients with public health insurance, remained, despite being corrected for age, gender, percentage of foreigners, and the type of general practice organization. Once community characteristics have been taken into account, it appears that demographic variables such as age and gender have the largest impact on the GP workload. Earlier studies have demonstrated that there is a difference between patients who receive public health insurance as opposed

**Table 4.5**

**Standardised coefficients of number of face to face contacts en episodes of RNG-data (multilevel regression) stratified by private insurance patients (ZF0) and public insurance patients (ZF1)**

| | | Number of face to face contacts | | Number of episodes | |
|---|---|---|---|---|---|
| | | Model ZF0 coefficient | Model ZF1 coefficient | Model ZF0 coefficient | Model ZF1 coefficient |
| **Levels** | Variables | | | | |
| **GP** | | | | | |
| | Organisation: soloist | 0.00 | -0.06 | -0.08 | -0.16 * |
| **Neighbourhood** | | | | | |
| | Deprived area | -0.001 | 0.06 * | -0.001 | 0.06 * |
| | % foreigners | -0.04 * | 0.01 | -0.04 * | 0.00 |
| **Patient** | | | | | |
| | Age (yr) | 0.21 * | 0.19 * | 0.20 * | 0.19 * |
| | Age-square | 0.16 * | 0.06 * | 0.11 * | 0.00 |
| | Over 65 years | -0.05 | -0.01 | -0.01 | 0.09 * |
| | Gender: women | 0.12 * | 0.14 * | 0.14 * | 0.18 * |
| | Interaction : | | | | |
| | Age and gender | 0.03 * | 0.01 | 0.04 * | 0.02 |

* $p < 0.05$



**Table 4.6**

**Standardised coefficients of the number of prescriptions of RNG-data and Geové-RZG-data (multilevel regression) stratified by private insurance patients (ZF0) and public insurance patients (ZF1)**

| | | RNG-data: Number of prescriptions | | Geové-RZG-data: Number of prescriptions |
|---|---|---|---|---|
| | | Model ZF0 coefficient | Model ZF1 coefficient | Model ZF1 coefficient |
| **Levels** | Variables | | | |
| **GP** | | | | |
| | Organisation: soloist | -0.10 * | -0.17 * | -0.02 |
| **Neighbourhood** | | | | |
| | Deprived area | -0.020 | 0.04 * | 0.027 * |
| | % Foreigners | -0.01 | 0.01 | 0.03 * |
| **Patiënt** | | | | |
| | Age (yr) | 0.36 * | 0.42 * | 0.50 * |
| | Age-square | 0.46 * | 0.07 * | 0.09 * |
| | Over 65 years | 0.12 * | 0.04 | -0.02 * |
| | Gender: women | 0.18 * | 0.20 * | 0.10 * |
| | Interaction : | | | |
| | age and gender | 0.00 | -0.04 * | -0.01 |

* $p < 0.05$

to those who are privately insured[12,23-27]. This supports discussions about socio-economic health differences in which it was concluded that one's neighborhood (or community) might be a determinant for the health of the inhabitants[28]. This has been termed the composition effect: the average health status for a community remains lower than that seen in other communities because of the composition of a particular neighborhood. Besides this composition effect, also a contextual effect has been observed. This means for example that a person's health may be influenced by living in a disadvantaged community[9,29]. More insight into these effects may be gained by looking at projects which have been developed and funded to help disadvantaged communities[30]. Our study shows that, even when age and gender are taken into account, treating patients who live in disadvantaged communities adds to the GP's workload. This is a contextual effect. This supports the idea that patients with public health insurance who live in disadvantaged communities contribute more to increase the GP's workload than patients with publicly funded health care who do not live in such communities[31].



The methods for defining disadvantaged communities were implemented in 1996 and revisited and revised in 1998[16]. The percentage of foreigners was added as a defining characteristic, whereas the number of inhabitants per square meter was no longer weighted as heavily, signifying that the degree of urbanization is no longer the unique and absolute criterion. Our analysis of the RNG data does not show a clear relationship between the percentage of foreigners and the GP workload. This may be due to the particular diversification and integration policies which are in effect in Groningen. Therefore, any concentration of foreigners in disadvantaged communities is not as evident as in the larger cities of the Randstad (this is the area in The Netherlands surrounding the cities of Amsterdam, Utrecht, Rotterdam, Den Haag, Amersfoort, Dordrecht, Hilversum, and Haarlem).

In the Geové-RZG data, a positive correlation was seen between the percentage of foreigners and the number of prescriptions. This finding indicates that an *foreigner* who visits his or her GP is more likely to receive a prescription than an indigenous resident[32-34].

In this study, the GP workload was only assessed with respect to activities directly involving the patient. It can therefore only approximate the actual workload of GPs. Other patient related factors such as continued education, ICT, teaching, and administrative duties which must be considered when determining the actual workload of the GP were not considered in this study[6,35,36]. The effect of the size of the practice was likewise not investigated. The data used for this study originated in a single geographical area from only seven GPs. The average number of patient-GP contacts found in this study is low compared to other studies[27,33,37]. We did not have access to the specific socio-economic status of each patient. Much research has shown that this is a prerequisite to identifying 'vulnerable groups' within GP practices. These are groups who, because of their social position, have limited access to intervention opportunities of both a preventive and a curative nature. We are dealing here with people whose financial problems, mental deficiencies, chronic unemployment, problems relating to addiction, and specific groups such as foreigners and illegal aliens.

The 'inverse care law' applies to the above identified special groups: *the*

*availability of good medical care tends to vary inversely with the need for it in the population served*[38,39].
With the help of contributions from the AOF, an attempt is being made to make working in disadvantaged communities more attractive[40]. This study shows that the age and the gender of the patient have a larger effect on increasing the GP's workload than their residency in a disadvantaged community. This could be an argument for placing greater emphasis on the age criterion when determining financial compensation for an increased workload.

### *4.6 Conclusion*



GPs face a larger workload in disadvantaged communities than they do in non-disadvantaged communities. The differences for patients with public health insurance living in disadvantaged communities remain even when the data are corrected for patient and community variables. Higher age in particular has an effect on the GP workload. The procedure of using aggregated data to identify disadvantaged communities is open for discussion, because both at the level of the GP and at a regional (postal code) level there is less variance than at the patient level. The opportunities for improving the algorithm are primarily found at the level of the patient. Our findings are based on a single city, which has already been addressing health issues caused by low socio-economic status, using the RNG database with data from a limited number of GPs. Both of these factors limit the external validity of the present results. This study could be replicated elsewhere in The Netherlands (i.e. by using the data from the second national NIVEL study) to check the validity of the results found in Groningen[37,41]. If these results were replicated, societal bodies would have to consider goal oriented improvements to the support systems required for physicians facing a higher workload.

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*Chapter 5*

# *Antibiotic prescribed patterns in the family practice setting*



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## *Abstract*

*Background:*
Although there are many antibiotic studies, a classification of the antibiotic prescribing over time in family practices with regard to all body systems is lacking.

*Objectives:*
(1) To identify prescribing patterns for patients receiving antibiotics in family practice. (2) To assess whether these patterns are stable across time, and to determine correlates of patient characteristics with these patterns.

*Methods:*
Data came from a morbidity and medication registration network of adult patients over the period 1998 – 2002. Latent class analysis was used to identify clusters of patients with similar antibiotic prescribing patterns.





*Subjects:*
A total of 125,707 observations were nested in 30,167 patients.

*Results:*
Interpretable three class models emerged for diagnostic indications involving the respiratory and urinary tract and the skin. A two-class model could be used for patients with indications involving the auditory system. Class 1 is a group of patients for whom no antibiotics were prescribed (non prescription group). Class 2 included patients who received less than one prescription per year with a total prescription number less than five for the duration of the study period (intermediate prescription group). Patients in class 3 received, on average, one to three prescriptions per year (high prescription group).

*Conclusions:*
This useful three-class structure shows relationships to sex, age, and socio-economic status of the patients. Women and the elderly received more antibiotic prescriptions, as did patients with a lower socio-economic status.



*Key words:*
prescription drugs, antibiotic use, practice variation, longitudinal models, latent class modeling

## 5.1 Introduction

Antibiotic use is lower in The Netherlands than anywhere else in Europe (ESAC-data 1997-2002)[1] and is estimated at 9.8 defined daily doses per 1,000 inhabitants per day. The number of antibiotics prescribed during the year 2000 was 0.4 per person. 80-86% of all antibiotics were prescribed by the family physicians.[2,3] Several studies during the past decade have evaluated family physician antibiotic prescribing patterns. Antibiotics are prescribed for a variety of indications, and most of these studies focused on a specific infection, disease, or complaint.[4-7] Cough, phlegm, rhonchi, cervical lymphadenopathy, and post-nasal drip are some of the symptoms associated with upper respiratory tract infections. Studies found these symptoms to account for many of the antibiotics prescribed by family physicians.[8-15] Also most studies are concerned with a specific indication (such as a urinary tract infection) or with a specific patient population (such as children). There are no studies in which a meaningful classification of antibiotic prescribing over time is evaluated with regard to all body systems. Most antibiotics are prescribed for complaints relating to the respiratory, urinary, auditory systems, and the skin, therefore these systems will be the focus of this study.



The aim of this study is to assess patterns of antibiotic prescribing by family physicians over time specified for morbidity specific factors. Three research questions will be answered:

1 Which pattern, if any, can be identified for patients receiving antibiotics in family practice setting?
2 Are these patterns stable across time, and do they have specific characteristics?
3 What are the pattern frequencies depending on patient characteristics?

An understanding of the long-term use of antibiotics may contribute to the fundamental and increasing bacterial resistance to antibiotics.

## 5.2 Methods

### 5.2.1 Study population

Starting in 1992, sixteen family physicians participated in the Morbidity and Medication Registration Network Groningen (RNG) of the Department of General Practice of the University of Groningen (UMCG). They registered all encounters with enrolled patients, specifically recording the diagnosis and any prescribed medication. The diagnoses were classified according to the International Classification of Primary Care (ICPC). The ICPC is based on body systems in a bi-axial classification structure, with the body systems on one axis (chapters having a letter code) and seven components of the other (having a two-digit numeric code).[16] In this study we use two components: component 1 provides terms for symptoms and complaints (code 01-29) and component 7 provides terms for well-defined diseases (code 70-99). Prescriptions were automatically coded according to the Anatomical Therapeutical Classification (ATC). ATC codes are alphanumeric and use seven positions. All antibiotic prescriptions for subjects 18 years and older registered with the RNG family practices from 1998 to December 2002 were included in this study. The sub-groups provided additional information on J01, the ATC code for antibiotics, specifying specific types of antibiotics. To determine whether results found for the study population could be applied to the general Dutch population, a comparison was made with results of previous studies.

### *5.2.2 Study Design*

The longitudinal data set (1998 – 2002) was used to assess intra- and interpatient variability. The dependent variable is the total number of antibiotic prescriptions per year per patient. The explanatory variables are those relating to the individual patient and those relating to the morbidity (specific disease groups) (Table 5.1).
In table 5.1, the following distinctions were made:

1 Variables at the patient level such as age, sex, type of insurance, and the duration of registration with the practice were recorded. Age was categorized into 10 year intervals, where the first category consisted of patients younger than 20 years, and the final category included those patients aged older than 90. Sex was expressed as a dummy variable (female = 1, male = 0). Type of insurance was also expressed as a dummy variable, with the value of one for public insurance (state funded) and zero for private insurance. This last variable is a proxy variable for socio-economic status of the patient (SES) (public = low, private = high). The variable 'duration' (as percentage) expressed the length of time a patient was registered with the practice. A value of 100 indicates that the patient was registered with the practice for the total duration of the study.
2 Variables at the prescription level included the following: specific ICPC chapter according to the primary diagnosis as recorded by the family physician. Most of the diagnoses fell into the four ICPC chapters for the respiratory, urinary, auditory systems, and the skin. The remaining diagnoses were grouped together as a miscellaneous group. We were therefore able to distinguish five separate groups: the four body systems and the miscellaneous group.



### *5.2.3 Statistical analysis*

In order to deal with unobserved heterogeneity in antibiotic prescribing, we applied mixture modeling with a latent class model (LCM).[17] From Deb[18] we adopted the hypothesis that the underlying unobserved heterogeneity which splits the patients into latent classes is based on an individual's latent long-term health status. 'Latent' refers to a characteristic that is not observed directly. Latent class analysis is based on the assumption that the observed dependent variable, which here is defined as antibiotic prescribing, can be represented by a model in which patients are divided into a number of groups, such that the dependent variable differs in average across groups, and is randomly distributed within groups.
The groups are called latent classes because group membership is not directly observed but can be inferred, with a margin of error from the observations of the dependent variable.
In this study, we will apply the first three of the four capabilities distinguished by Nagin[19] with relation to latent class modeling:

1 Identify distinct groups of patterns.
2 Estimate the proportion of the population according to each trajectory group.
3 Relate group membership probability to individual characteristics and circumstances.

**Table 5.1**

**Description of the data set**

| **Explanatory variables :** Patient characteristics | All patients in 5 years | Patients who received one or more prescription(s) for antibiotics during the 5 years |
|---|---|---|
| Number | 30167 | 12415 |
| Mean age(std) (in years) | 44.2 (18.1) | 48.7 (19.5) |
| Women (percentage) | 52.7 % | 61.2 % |
| Insured (percentage) | 53.5 % | 61.7 % |
| Mean duration in study (percentage) (std)a | 78.96 % (31.2) | 87.51 % (23.7) |
| | | |
| **Diagnosis groups** | | |
| Respiratory system | 26.1 % | 63.4 % |
| Urinary tract | 14.2 % | 34.5 % |
| Dermatological system | 6.7 % | 16.4 % |
| Auditory system | 1.9 % | 4.7 % |
| Miscellaneous group | 8.0 % | 19.5 % |

std = standard deviation; [a] reports the mean over five years

4 Use the group membership probabilities for various other purposes such as creating profiles of group members.

LCM provides a good framework with which we can distinguish between groups with high and low average antibiotic prescriptions.[20] As this methodology has not yet been widely applied, we also wanted to determine its feasibility in the study of antibiotic prescribing.

We used a Poisson distribution with overdispersion for this analysis because the dependent variable was a count. For the counts per patient per year we assumed a negative binomial distribution, which can be regarded as an overdispersed Poisson distribution.[21] In this case the count has a basic Poisson distribution with a Poisson rate that has a gamma distribution with variance $\sigma^2$. The expected value of the count distribution depended on the latent class. The overdispersion parameter $\sigma^2$ was assumed to be constant across the latent classes. Models were tested both with latent classes that had constant rates across the years, and with classes where rates fluctuated over the years.

To determine the number of classes, we used the Bayesian information criterion (BIC).[17] To answer the research questions, latent class modeling was done with the use of the computer program LatentGOLD.[22] A separate model was used for each of the five ICPC chapters. Mixture Poisson models with five year predictor periods as dummies were applied, with the following specifications: overdispersion, equal dispersion across the classes, and class dependency for the time-predictor. Models with fluctuating rates within classes did not have better BIC values than models with constant rates, and therefore the constant rate models are presented here. For the patients who were in the registration an offset was used in the logarithm of the expected value. For a more extended discussion of the method of latent class analysis the reader is referred to Vermunt and Magidson.[23]

**Table 5.2**

**Estimated latent class rates and class proportions for the classes determined by latent class analysis**

| | Rates | | | Proportions | | |
|---|---|---|---|---|---|---|
| | Class 1 | Class 2 | Class 3 | Class 1 | Class 2 | Class 3 |
| ICPC- chapters : | | | | | | |
| Respiratory | 0.029 | 0.380 | 1.752 | 74.8 | 22.4 | 2.9 |
| Urinary | 0.010 | 0.424 | 2.525 | 84.9 | 13.3 | 1.9 |
| Dermatology | 0.007 | 0.149 | 1.154 | 88.4 | 11.1 | 0.5 |
| Auditory | 0.002 | 0.093 | | 94.9 | 5.1 | |
| Miscellaneous group | 0.002 | 0.113 | 0.804 | 76.8 | 22.6 | 0.7 |

## 5.3 Results

### 5.3.1 Patient characteristics

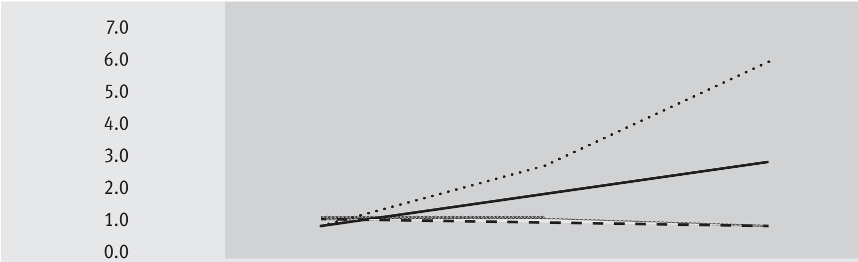
30,167 patients, aged 18 to 102 years, were included in this study. To 41.2% of these patients antibiotics were prescribed at some point during the five-year period of the study. The mean age was 44 years, and 53% of patients were women (Table 5.1). The mean registration time for all patients was 79%, with 59% of patients registered for the full five years. More than 50% of patients had public health insurance. To estimate the degree to which the sample of this study accurately reflects the overall demographic in the Netherlands, three patient characteristics (age, sex and insurance status) are compared between this study and Statistics Netherlands in 2001. Statistics Netherlands is a Dutch governmental institution that gathers statistical information about the Netherlands. Based on the total number of patients of this study, the number of patients over 65 years is 11.0%, the number of female in terms of percentage is 51.5%, and number of patients who are public insured is 54.4%. Derived from Statistics Netherlands the numbers for age, sex and insurance state in terms of percentage are 13.6%, 50.5% and 64.1% respectively. Our study population has lower numbers of people who are publicly insured and of elderly. Women are over-represented in the study group.
Table 5.1 shows that about two-thirds of patients for whom antibiotics were prescribed received these for respiratory system indications, while about one-third of patients received them for urinary system indications. The biggest overlap was seen between the respiratory and urinary tract body systems. Four percent of patients had both diagnoses relating to the urinary and respiratory tract (not presented).

### 5.3.2 Latent class analysis

We initially determined the number of latent classes using the Bayesian Information Criterion.[17] The smallest BIC values were obtained for the following numbers of classes: five for the respiratory ICPC chapter, six for the urinary chapter, three for the skin chapter, two for the auditory ICPC chapter, and three for the remaining miscellaneous category. For the respiratory and urinary tract systems, the results led to models that seemed to overfit the data; this is understandable in view of the large number of cases. We therefore decided to determine numbers of classes giving a good fit while at the same time leading to a clear clinical interpretation. When increasing the number of classes from two to higher values, the main decreases in BIC were obtained for an increase to

**Figure 5.1**

**Odds of gender in three classes for the four body-systems and the miscellaneous group (reference-category: male)**




| | 1 | 2 | 3 |
|---|---|---|---|
| Respiratory | 1.0 | 1.3 | 1.6 |
| Urinary | 1.0 | 2.8 | 6.1 |
| Skin | 1.1 | 1.1 | 1.0 |
| Auditory | 1.1 | 1.1 | |
| Miscellaneous | 1.1 | 1.1 | 1.0 |

three classes for the respiratory and urinary ICPC chapters. In all of these cases, any further increase in the number of classes led to differentiation within the classes of patients who received prescriptions at least once during the observation period, but with an average number of prescriptions of hardly more than one per year. This seemed to be a differentiation, which is not meaningful clinically, and was therefore not pursued by us. The results presented here are for the 2-class (for auditory) and 3-class solutions (for respiratory, urinary, skin, and the miscellaneous group), which were best interpretable. The estimated prescribing rates and frequencies of the latent classes were calculated and are presented in table 5.2. The estimated Poisson rates in the three-class model of the respiratory body system were 0.03, 0.38, and 1.75, and the frequencies were 0.75, 0.22, and 0.03. This means that class 1 consisted of 75% of the patients and they received an average of 0.03 antibiotic prescriptions per year. The average number of prescribed antibiotics in class 2 (22% of the patients) was 0.38, and in class 3 (3% of the patients) it was 1.75.

Table 5.2 shows that the rates in class 1 are very low for all ICPC chapters (0.002-0.029). This class can be described as the class of patients for whom no antibiotics were prescribed (non prescription) or only very rarely. Class 3 is the group containing patients who received more than one antibiotic prescription per year. This group can be described as the high prescription group. The rates in class 2 are intermediate between classes 1 and 3. These patients did not receive a prescription each year, but received some amount greater than zero and less than five for the complete five-year period. We called this group the varied prescription group.

The sequence of the three classes (class 1 = non prescription, class 2 = varied prescription, and class 3 = high prescription) shows an ascending progression of prescribing.

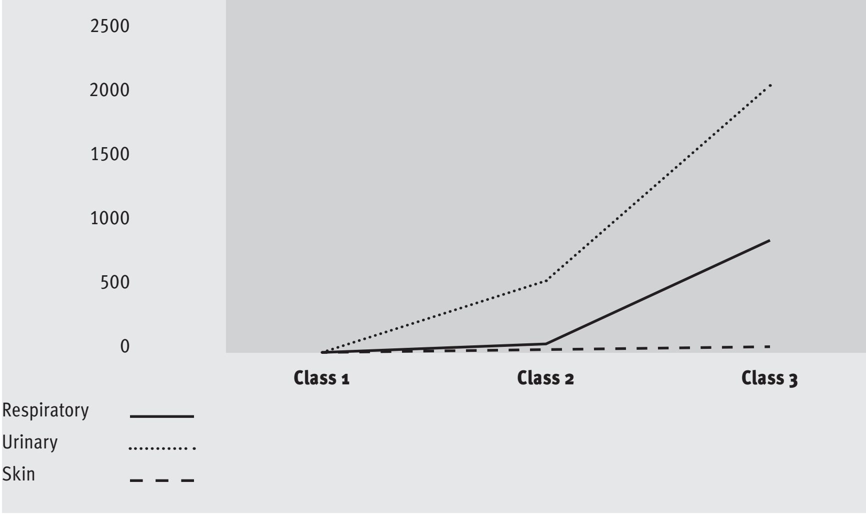
**Table 5.3**

**Proportion of the patient characteristics (gender, age and socio-economic status (SES)) in the three classes per body-system**

| | | Respiratory Class | | | Urinary Class | | | Skin Class | | | Auditory Class | | Miscellaneous group Class | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 1 | 2 | 3 |
| **Gender** | | | | | | | | | | | | | | | |
| | Male | 0.49 | 0.43 | 0.38 | 0.51 | 0.26 | 0.14 | 0.47 | 0.47 | 0.49 | 0.47 | 0.47 | 0.48 | 0.47 | 0.51 |
| | Female | 0.51 | 0.57 | 0.62 | 0.49 | 0.74 | 0.86 | 0.53 | 0.53 | 0.51 | 0.53 | 0.53 | 0.52 | 0.53 | 0.49 |
| **Age-group** | | | | | | | | | | | | | | | |
| | ‹20 | 0.03 | 0.03 | 0.01 | 0.03 | 0.02 | 0.01 | 0.03 | 0.02 | 0.02 | 0.03 | 0.03 | 0.03 | 0.03 | 0.02 |
| | 20-29 | 0.23 | 0.17 | 0.09 | 0.21 | 0.21 | 0.15 | 0.21 | 0.19 | 0.20 | 0.21 | 0.21 | 0.21 | 0.20 | 0.15 |
| | 30-39 | 0.25 | 0.22 | 0.16 | 0.25 | 0.20 | 0.11 | 0.24 | 0.23 | 0.20 | 0.24 | 0.24 | 0.24 | 0.24 | 0.20 |
| | 40-49 | 0.19 | 0.19 | 0.17 | 0.19 | 0.14 | 0.09 | 0.19 | 0.18 | 0.17 | 0.19 | 0.19 | 0.19 | 0.18 | 0.18 |
| | 50-59 | 0.14 | 0.15 | 0.17 | 0.14 | 0.12 | 0.10 | 0.14 | 0.14 | 0.15 | 0.14 | 0.14 | 0.14 | 0.14 | 0.18 |
| | 60-69 | 0.07 | 0.09 | 0.13 | 0.07 | 0.08 | 0.11 | 0.08 | 0.08 | 0.07 | 0.08 | 0.08 | 0.07 | 0.08 | 0.10 |
| | 70-79 | 0.06 | 0.08 | 0.14 | 0.06 | 0.10 | 0.15 | 0.06 | 0.07 | 0.10 | 0.06 | 0.07 | 0.06 | 0.07 | 0.10 |
| | 80-89 | 0.04 | 0.06 | 0.10 | 0.03 | 0.08 | 0.19 | 0.04 | 0.06 | 0.06 | 0.04 | 0.04 | 0.04 | 0.05 | 0.06 |
| | ›90 | 0.01 | 0.02 | 0.04 | 0.01 | 0.03 | 0.09 | 0.01 | 0.02 | 0.04 | 0.01 | 0.01 | 0.01 | 0.01 | 0.02 |
| **SES** | | | | | | | | | | | | | | | |
| | High | 0.49 | 0.41 | 0.32 | 0.48 | 0.40 | 0.29 | 0.47 | 0.44 | 0.38 | 0.47 | 0.45 | 0.47 | 0.44 | 0.40 |
| | Low | 0.51 | 0.59 | 0.68 | 0.52 | 0.60 | 0.71 | 0.53 | 0.56 | 0.62 | 0.53 | 0.55 | 0.53 | 0.56 | 0.60 |

**Figure 5.2**

**Odds ratios of having well-defined diseases versus complaints (as reference category) indication in the three latent classes for respiratory, urinary and dermatology systems**




*5.3.3 Group membership related patient characteristics*

In table 5.3, the patients' demographic characteristics are related to their positioning within the three classes. Women make up more than 50% of all the classes of the five ICPC chapters. Women receive more prescriptions than men. In figure 5.1, the odds ratios (with men as reference category) of the three classes are represented from table 5.3. The elderly show the greatest representation in class 3 (high prescription group). More than 50% of each class is made up of patients from the lower SES as determined by health insurance coverage. They make up about 50% of class 1 and more than 60% of class 3.

In figure 5.1 we see that the respiratory and urinary tract ICPC chapters are distinct from the other ICPC chapters because of an increasing odds-trend. The urinary tract ICPC chapter's odds ratio increases more than the one for the respiratory system. The other ICPC chapters all have odds ratios around 1. Odds ratios greater than 1 signify that more prescriptions are written for women than for men.

With respect to SES (in which the high SES group is the reference category), it can also be seen that the odds ratios increase with an ascending progression of the latent classes. Therefore, in cases of low SES, the prescribing rate is higher than for the higher SES group. Whether or not complaints occur with relation to diseases in the three latent classes is explored in figure 5.2. Odds ratios for the respiratory, urinary and dermatology chapters shows this relationship.

## *5.4 Discussion*

A pattern of three classes of antibiotic prescribing was identified in this study population, which takes into account the respiratory, urinary, auditory, and dermatological systems as well as a miscellaneous group. The three classes

include class 1, the non prescription group; class 2, the varied prescription group; and class 3, the high prescription group. No class 3 group was identified for the auditory ICPC chapter. This was due to the low prevalence of ear related infections in age groups older than 18 years. This agrees with the prescription pattern of antibiotics in The Netherlands which shows that prescriptions relating to the auditory system are very low in populations of patients aged 18 years and older.[1,24]
A comparison of the two largest ICPC chapters for which antibiotics are prescribed, namely the respiratory and urinary tracts, revealed that 75% of respiratory patients and 85% of the urinary tract patients were in class 1. The number of antibiotic prescriptions for class 2 was 0.4 for both the respiratory and the urinary tract ICPC chapters. An average of one prescription per year was prescribed for patients in class 2. There were differences between the respiratory and urinary groups for class 3. More prescriptions were written for indications involving diseases of the urinary tract, but for fewer patients. This could be the result of prescribing a number of courses of antibiotics for urinary tract infections for these patients. The fact that we did not find any fluctuation over time was likely caused by the relatively stable rates of antibiotic prescribing seen between 1992 and 2001. Kuyvenhoven reported that the number of antibiotic prescriptions has been rather stable since the early 1990s in The Netherlands, whereas these rates have decreased in the United Kingdom and in the United States. [25] This stable prescription rate likely accounts for there being no clearly identifiable fluctuations during our study period from 1998-2002. To distinguish clear fluctuations, a longer study period would be required.



Gender was the focus of 11 studies. In five of these, it was found that more antibiotics were prescribed for women.[7,13,26-28] Straand et al [28] reported that 61% of women received prescriptions for antibiotics which is supported by our findings. Sorenson [29] mentioned a relationship between gender and antibiotic prescriptions, but did not explain any further. Five of the studies concluded that gender did not affect prescription rates for antibiotics. [5,30-33] In our study, for 63% of the patients who received antibiotics prescriptions, the indication involved the respiratory tract. Other studies have reported between 60% and 70%.[34,35]
We confine ourselves to the results seen in class 3, as this is the most relevant class of patients for the family physician. From table 5.2 it is apparent that the highest percentages of patients in class 3 have well defined diseases from the respiratory and urinary tract ICPC chapters; 2.9% and 1.9% respectively. 42 patients fell into both categories. *T*hese patients represent a small group of mainly women who are public insured (low SES), and elderly who have well defined diseases.

### *5.4.1 Limitations and strengths*

McManus reported a seasonal fluctuation in the rates of prescribing antibiotics.[10] We have not addressed this point, as our data were aggregated into numbers per year.
One of the strengths of this study is that the diagnostic indication was actually linked to the antibiotic prescription. This clearly produces more meaningful results than those that would be obtained by using data from a pharmacy database. One of the limitations of this study is that patients who received antibiotic prescription from the specialist are not represented.

### 5.4.2 Conclusions

In conclusion, this study models antibiotic prescribing patterns along with the diagnostic indications for a population of adult patients registered with family physicians during a five-year period. A three-class structure was apparent for the respiratory, urinary, and dermatological body systems. Only two classes were identified for the auditory system, which has a lower prevalence. The remaining diagnoses were grouped together as a miscellaneous-group, and also showed the three-class structure.

This class structure consists of a group of patients for whom few or no antibiotics were prescribed (class 1), a group of patients for whom antibiotics were prescribed from time to time on average less than 1 per year (class 2), and for the respiratory, urinary, and dermatological body systems a group of patients for whom antibiotics were regularly prescribed (class 3). Class 1 consists of the largest group of patients varying between 75% and 95%. Class 2 varies from 5 to 25%, and class 3 varies between 0.5% and 3%. There is a relationship between gender, age, and SES and class of antibiotic prescribing. More antibiotics are prescribed for women, the elderly, and patients with a low SES. This pattern of a three-class structure should be reinvestigated in a future study with an extension of the covariates before any results can be applied in health care and policy.

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*Chapter 6*

# *General practitioners reduced benzo-diazepine prescriptions in an intervention study: a multilevel application*



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***Abstract***

*Objective:*
This study investigated the effects of general practitioner, patient, and prescription characteristics on the reduction of long-term benzodiazepine prescribing by sending a letter to chronic users. The data were analyzed with a method respecting the hierarchical data structure.

*Study Design and Setting:*
Data were obtained from 8,170 chronic users nested in 147 general practices. One thousand two hundred fifty-six chronic users in 19 general practices received a letter with the advice to reduce or stop the use of benzodiazepines after the general practitioners had attended a course on benzodiazepine use. In a three-level random intercept multilevel regression model, long-term prescribing of benzodiazepines was the dependent variable.



*Results:*
The reduction in benzodiazepine prescribing was significantly larger in the intervention than in the control group: 16% after 6 months and 14% after 12 months, respectively. The age of the patient, gender, and the interaction between age and gender were significant. The combination of the duration (long acting or short acting) with the type of benzodiazepine (anxiolytic or hypnotic) was an important pharmacological baseline covariate.

*Conclusions:*
The reduction of benzodiazepine prescribing was mainly explained by the letter intervention and individual patient characteristics. Multilevel analysis was a worthwhile method for application in this study with its unbalanced design.

*Keywords:*
Benzodiazepine use; Intervention study; Multilevel modelling; General practitioner; Chronic user; Long-term prescription

## *6.1 Introduction*

Benzodiazepines are the most widely prescribed drugs for a variety of conditions, particularly insomnia, anxiety disorders and disorders associated with psychiatric conditions[1-4]. The prevalence rate of benzodiazepine-use varies from 2.2 – 17.6%[5,6]. Long-term benzodiazepine use has negative health effects[7,8]. In some studies an attempt is made to reduce the high prevalence or to stop the benzodiazepine-use in general practices by sending a letter to patients[9-11].
Egan et al.[12] demonstrates that patient factors should be taken into account to estimate the association between general practitioner factors and the use of long-acting benzodiazepines. A lot of studies report that patient age, in particular older age has a relation to the use of benzodiazepines[3,13-16].
Holden et al find that younger patients are significantly more likely than those over the age of 65 to stop benzodiazepines [14]. Cormack indicates that a simple intervention such as a letter from the general practitioner can have considerable effect on the use of hypnotic and anxiolytic drugs, also when the sample consists of elderly users[17]. He also concludes that the use of benzodiazepine is reduced up to 30%, compared with the use in a control group. Morgan[11] based on Cormack[9] describes the economic advantages. Apart from the reduction of the use of benzodiazepine, Bashir[18] shows that there is an increase of antidepressiva accompanying the reduction of benzodiazepine use.
Isacson[15] shows that the following factors predicting long-term benzodiazepine-use are: age, a combined use of tranquilizers and hypnotics, and prescriptions from more than one doctor. According to Morrison[19] an intervention is worthwhile and the increase in workload is very small. The intervention implies that the patient is asked to discontinue the use of benzodiazepines with the help of the general practitioner. Other studies [7,13,20-22]underline the role of the general practitioner.

### *6.1.1 Present investigation*

With regard to all these studies concerning the use of benzodiazepine three groups of characteristics are distinguished:

1 patient characteristics as age and gender
2 prescription characteristics, e.g. duration
3 general practitioner characteristics as workload.

Since prescription, patient, and general practitioner are hierarchically related – patients are nested under general practitioners and prescriptions under patients – a multilevel approach is an appropriate technique of analysis[23-28].
Because we are interested in reducing the chronic use of benzodiazepines we initiated a study with following research question: what is the influence of sending an educational letter to patients on the reduction of long-term benzodiazepine prescribing, controlled for general practitioner, patient, and prescription characteristics?

## *6.2 Methods*

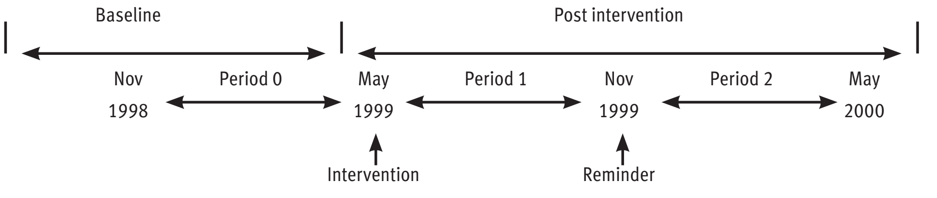
*6.2.1 Study sample*

All general practitioners in the northern and eastern part of the province of Groningen in the Netherlands with chronic users of benzodiazepine are candidates for inclusion in the study. In this rural region the use of benzodiazepines is very high, according to local reports[29]. The chronic benzodiazepine users, who are included in the study, are patients who obtain at least 180 defined daily doses (DDD) of benzodiazepine in the course of one year (November 1997 – November 1998). The patients are extracted from the administrative database of the largest health insurance company. Patients who transferred from the insurance company or from one general practitioner to another general practitioner (not included in the study) and patients who died are excluded from the analysis.

**Figure 6.1**



**Design of the study**




*6.2.2 Intervention and control group*

In this study, two groups of chronic benzodiazepine-users are compared. The allocation of patients to one of the two groups takes place at the general practitioner level. The intervention group receives a letter of the general practitioner with the request to stop or to reduce their benzodiazepine use. The control group does not receive a letter. All general practitioners from the intervention group and a selection of the control group were offered a postgraduate course, including information about the pharmacokinetics of benzodiazepines and a schedule for slow reduction of benzodiazepine-use to prevent withdrawal symptoms. The trial is described on detail elsewhere[30]. The research period includes one and half year (from November 1998 – May 2000) during which an intervention in May 1999 was accomplished (Figure 6.1). The intervention implies that a letter was sent by the general practitioner to the chronic users with information about the risks of continuous use and the advice to reduce or to stop the use of benzodiazepine. In November 1999 a random selection of the general practitioner practices sent a reminder to those patients who did not react on the first letter.

*6.2.3 Outcome*

The study period from November 1998 to May 2000 consists of three periods: 1) baseline period from November 1998 to May 1999, 2) post-intervention period 1 from May 1999 to November 1999 and 3) post-intervention period 2 from November

1999 to May 2000 (Figure 6.1). The outcome in this study is the sum of the defined daily doses of benzodiazepine prescriptions per period prescribed by the general practitioner per patient. The defined daily dose is the assumed average maintenance dose per day for a drug used for its main indication in adults[31]. According to the Anatomical Therapeutic Chemical classification system (ATC) all drugs are classified and benzodiazepines are defined by the codes N05BA, N05CD, and N05CF[32].

*6.2.4 Statistical analysis*

The primary outcome is the sum of prescribed number of DDD's per patient per half year, controlled for general practitioner, patient and prescription characteristics. The influence of these characteristics will be analysed by means of multilevel modelling.

The general practitioners characteristics are: belonging to the course or the non-course group, belonging to the intervention or control group, and the sending of a reminder or not.



The patient characteristics are age and gender. Age is centred around the grand mean.

Prescribing characteristics are the duration of effectiveness (long acting versus short acting benzodiazepine) and the type of benzodiazepine (hypnotic or anxiolytic) as indicated by the total of prescribed benzodiazepines in the baseline period. Long-acting benzodiazepines include chlordiazepoxide, diazepam, flurazepam and nitrazepam. Shorter-acting benzodiazepines are alprazolam, bromazepam, lorazepam, temazepam en triazolam. The dummy variables of the prescription characteristics are the combination of the duration of effectiveness (long acting or short acting) and the type of benzodiazepine (hypnotics or anxiolytics). Per period the prescription characteristics are aggregated to patient level (pharmacological variables). In Table 6.1 a summary of these dummy variables is given with the number of patients. The reference category is the group patients which use long acting anxiolytics and short acting hypnotics.

*6.2.5 Multilevel model*

A three-level random intercept multilevel regression model will be used with periods nested within patients nested within general practitioners. This multilevel model is used to assess the effects of general practitioner, patient, and prescription characteristics on the defined daily dosage of benzodiazepines. The first step is a null model which serves as a baseline for other models. This null model (Model 0) reflects the situation of figure 6.1 but without the intervention and the two groups. The next model (Model 1) adds the effects of the intervention. Baseline and the post-intervention periods are estimated in Model 1 and also the differences between baseline and post-intervention periods as a result of the letter in the intervention and control group. Next, Model 2 is fitted with all remaining general practitioner, patient characteristics, and theoretically relevant interactions. The patient characteristics include variables which are directly related to the patient and variables which are indirectly related. Age and gender are directly related variables. Examples of the indirectly related variables are prescription characteristics, aggregated to patient level as anxiolytics and

**Table 6.1**

**Description of general practice characteristics at general practice level, and patient characteristics at patient level. (Total, percentage, mean, and standard deviation)**

| **General Practice characteristics** | N = 147 | |
|---|---|---|
| Allocation: | | |
| Intervention | 19 | (12.9%) |
| Control (ref.) | 128 | (87.1%) |
| Education group: | | |
| Course group | 56 | (38.1%) |
| Non-course group (ref.) | 91 | (61.9%) |
| Reminder letter: | | |
| Yes | 9 | (6.1%) |
| No (ref.) | 138 | (93.9%) |
| | | |
| **Patient characteristics** | N = 8170 | |
| Gender: | | |
| Female | 5978 | (73.2%) |
| Male (ref.) | 2192 | (26.8%) |
| Age (years) | mean = 64.63 | (std. = 14.97) |

| Prescription characteristics (Number of patients (percentage)) aggregated at patient level (pharmacological variables) | | |
|---|---|---|
| Hypnotic Short-acting (HS) only | 2396 | (29.33%) |
| Hypnotic Long-acting (HL) only | 965 | (11.81%) |
| Anxiolytic Short-acting (AS) only | 1455 | (17.81%) |
| Anxiolytic Long-acting (AL) only | 1025 | (12.55%) |
| Hypnotic Short-acting + Hypnotic Long-acting (HS + HL) | 63 | (0.77%) |
| Anxiolytic Short-acting + Anxiolytic Longacting (AS + AL) | 194 | (2.37%) |
| Hypnotic Short-acting + Anxiolytic Short-acting (HS + AS) | 989 | (12.11%) |
| Hypnotic Long-acting + Anxiolytic Long-acting (HL + AL) | 140 | (1.71%) |
| Hypnotic Long-acting + Anxiolytic Short-acting (HL + AS) | 279 | (3.41%) |
| Hypnotic Short-acting + Anxiolytic Long-acting (HS + AL) (ref.) | 441 | (5.40%) |
| Hypnotic Short-acting + Hypnotic Long-acting + Anxiolytic Short-acting (HS + HL + AS) | 56 | (0.69%) |
| Hypnotic Short-acting + Hypnotic Long-acting + Anxiolytic Long-acting (HS + HL + AL) | 13 | (0.16%) |
| Hypnotic Short-acting + Anxiolytic Short-acting + Anxiolytic Long-acting (HS + AS + AL) | 106 | (1.30%) |
| Hypnotic Long-acting + Anxiolytic Short-acting + Anxiolytic Long-acting (HL + AS + AL) | 34 | (0.42%) |
| Hypnotic Short-acting + Hypnotic Long-acting + Anxiolytic Short-acting + Anxiolytic Long-acting (HS + HL + AS + AL) | 14 | (0.17%) |
| | 8170 | (100%) |

Abbreviations: std. = standard deviation; ref. = reference category hypnotics, which can be short acting as well as long acting. The prescription characteristics aggregated to patient level are intended to control for the effect of baseline prescribing. Differences between subsequently fitted models are tested by deviance (i.e. likelihood ratio) chi-squared tests. Also the explained variance and t-ratio of the estimates will be calculated. The significance level used is 0.05. The fixed and random parts are modelled using dummy variables for baseline, post-intervention period 1, and post-intervention period 2, defined mutually exclusively so that for each data point exactly one of the three dummy variables is 1. These dummy variables have random effects at level two (patient level) and level three (general practitioner level). There is no random part at level one[28]. The SAS statistical package (Proc Mixed)[33] and the multilevel program MLwiN[34] are used in order to analyse the data.

## 6.3 Results



### 6.3.1 Characteristics of the population

Of the 147 general practitioners, 19 general practitioners (13%) are allocated to the intervention group and, 128 to the control group. About one third of the general practitioners (38.1%) followed the course on reducing benzodiazepine use, namely all general practitioners of the intervention group and 37 (29%) of the control group. (Table 6.1) The total number of patients is 8170 (about 65 patients per general practitioner, range 7-251). The mean age of the 8170 patients is 65 year. In the baseline period the percentage of only long-acting benzodiazepine users is 26%, the percentage of only short-acting benzodiazepine users is 59% and the percentage of both long and short acting users is 15%. The prescribing of the two type of benzodiazepines, hypnotics or anxiolytics only are respectively 42% and 33%, while both hypnotics and anxiolytics are prescribed to 25% of the patients. In Table 6.1 the 15 different kind of users are specified, which will be used in the analysis. The combination short-acting hypnotic and long-acting anxiolytic will be the reference category. The percentage patients using psychofarmaca is seven percent in the baseline period. The mean defined daily dosage of benzodiazepines in the intervention-group at the baseline period is 207.4, decreasing to 197.2 in post-intervention period 1 and increasing to 200.49 in post-intervention period 2; in the control group these values are 203.5, 208.4 and 205.3 respectively (Table 6.1). Since the distribution of defined daily dosage is skewed, a log transformation was applied. After the log transformation no relapse is found in the intervention group with regard to post intervention period 2.

### 6.3.2 Multilevel analysis

Table 6.2 (Model 0 to Model 2) shows the results obtain from multilevel analysis. Model 0 is the null model. The estimate 'Baseline' in Model 0 is the maximum likelihood estimate for mean defined daily dosage in the baseline period. This estimate is transformed and becomes 163.36 (an antilog transformation of the estimate baseline is $e^{5.096}$). This mean of 163.36 DDD can be interpreted as the expected total of the defined daily dosage in the baseline period of a random patient prescribed by a random general practitioner. Six month and a year

**Table 6.2**

**Statistics (mean(std.) and median (IQR)) of defined daily dosages (DDDs) of benzodiazepines at baseline, post intervention 1, and post intervention 2 periods**

| | | Baseline | Post – Intervention 1 | Post-Intervention 2 |
|---|---|---|---|---|
| **Intervention group** | | | | |
| | Mean (std.) | 207.33 (155.64) | 196.44 (172.42) | 199.84 (174.81) |
| | median (IQR) | 180.27 (130.99) | 163.02 (133.90) | 168.02 (145.36) |
| **Control group** | | | | |
| | Mean (std.) | 203.50 (160.95) | 207.49 (168.00) | 204.28 (163.84) |
| | median (IQR) | 180.27 (119.30) | 180.27 (130.90) | 180.27 (130.99) |

std. = standard deviation; IQR = inter-quartile range



later the mean becomes respectively, 157.43 DDD and 153.70 DDD. The random parameters in Model 0 express the between-patient variability at patient level and the between-general practitioner variability at general practitioner level. They indicate that most of the variation of the defined daily dosage is at patient level.
In Model 1 (Table 6.2) the effect of the letter (intervention) is estimated in post intervention period 1 and 2 by the interaction parameters 'intervention by post period 1 and post period 2' respectively. The reduction obtained by the letter is significant in period 1 ($t = -12.30$, $p<0.05$) and also in period 2 ($t = -10.34$, $p<0.05$). Comparing the intervention group to the control group, a reduction of $((1-e^{-0.175})*100) = 16\%$ appears after a half year and 15.6% after one year. The finding that the intervention parameter (estimate = 0.03, $t= 1.01$, $p>0.05$) is not significant in this model, indicates that there is no difference between the intervention group and the control group in the baseline period. In Model 1, the explained variance at general practitioner level in the post intervention period 1 and 2 is 27% and 25% respectively.
In Model 2 the general practitioner and patient characteristics, the prescription characteristics aggregated to patient level and interactions terms are included. All patient characteristics are significant as well as the interaction term 'age by gender'. The informed general practitioners (education group) differ from the non-informed general practitioners ($t=-3.05$, $p<0.05$). The significant pharmacological variables include: the four main kinds of benzodiazepines (the prescribing of only: 1. short-acting hypnotic (HS), 2. long-acting hypnotic (HL), 3. short-acting anxiolytic (AS), and 4. long-acting anxiolytic (AL)), three combinations of two benzodiazepines (1. HS + HL, 2. AS + AL, and 3. HS + AS), a combination of three benzodiazepines (HL + AS + AL), and the combination of four benzodiazepines (HS + HL + AS + AL). Psychiatric medication is not significantly related with the sum of defined daily dose of the baseline period. After adjusting for all variables, the reduction of defined daily doses is 16% after a half year and 14% after one year. The explained variances of Model 2 on general practitioner level for the three periods baseline, post intervention period 1 and post intervention period 2 are respectively 22%, 44% and 37%, and at patient level respectively 8%, 5% and 5%. As a result of the letter intervention, a change can be seen between baseline and post intervention period 1. The correlation between this change and the baseline is -0.12 as calculated from the variance/covariance at patient level. In figure 6.2 is

**Table 6.3**

**Parameter estimates (standard errors and t-values) of general practice, patient and period characteristics of three multilevel models**

| | Model 0 | | | Model 1 | | | Model 2 | | |
|---|---|---|---|---|---|---|---|---|---|
| Fixed | estimate | s.e. | | estimate | s.e. | | estimate | s.e. | |
| General Practice level | | | | | | | | | |
| Intervention (vs control) | | | | -0.002 | 0.033 | | -0.022 | 0.039 | |
| Education group (vs non education) | | | | 0.049 | 0.023 | * | 0.045 | 0.022 | * |
| Reminder-letter yes (vs no) | | | | | | | 0.004 | 0.051 | |
| **Patient Level** | | | | | | | | | |
| Female (vs Male) | | | | | | | -0.047 | 0.015 | ** |
| Age (years) | | | | | | | -0.005 | 0.0009 | *** |
| Period level | | | | | | | | | |
| Baseline | 5.096 | 0.011 | *** | 5.075 | 0.014 | *** | 5.433 | 0.033 | *** |
| Post-intervention period 1 | 5.059 | 0.012 | *** | 5.064 | 0.014 | *** | 5.421 | 0.033 | *** |
| Post-intervention period 2 | 5.035 | 0.013 | *** | 5.039 | 0.015 | *** | 5.396 | 0.034 | *** |
| Anti-depressant yes (vs no) | | | | | | | -0.042 | 0.027 | |
| **Interactions:** | | | | | | | | | |
| Gender * Age | | | | | | | 0.004 | 0.001 | *** |
| Intervention * post period 1 | | | | -0.175 | 0.014 | *** | -0.176 | 0.014 | *** |
| Intervention * post period 2 | | | | -0.170 | 0.016 | *** | -0.155 | 0.02 | *** |
| Post period 2 * Reminder-letter | | | | | | | -0.032 | 0.025 | |
| Hypnotic short-acting [HS] only | | | | | | | -0.417 | 0.031 | *** |
| Hypnotic long-acting [HL] only | | | | | | | -0.385 | 0.035 | *** |
| Anxiolytic short-acting [AS] only | | | | | | | -0.378 | 0.033 | *** |
| Anxiolytic long-acting [AL] only | | | | | | | -0.479 | 0.034 | *** |
| HS + HL | | | | | | | -0.26 | 0.079 | *** |
| AS + AL | | | | | | | -0.307 | 0.052 | *** |
| HS + AS | | | | | | | -0.086 | 0.034 | ** |
| HL + AL | | | | | | | -0.014 | 0.058 | |
| HL + AS | | | | | | | -0.064 | 0.046 | |
| HS + AL | | | | | | | 0 | | |
| HS + HL + AS | | | | | | | 0.027 | 0.085 | |
| HS + HL + AL | | | | | | | 0.299 | 0.169 | * |
| HS + AS + AL | | | | | | | 0.046 | 0.065 | |
| HL + AS + AL | | | | | | | 0.278 | 0.107 | * |
| HS + HL + AS + AL | | | | | | | -0.338 | 0.163 | * |
| **Random** | | | | | | | | | |
| *Level: General Practice:* | | | | | | | | | |
| *Variance / covariance* | Baseline | PIP-1 | PIP-2 | Baseline | PIP-1 | PIP-2 | Baseline | PIP-1 | PIP-2 |
| Baseline | 0.008 | | | 0.007 | | | 0.006 | | |
| Post-intervention period 1 (PIP-1) | 0.007 | 0.011 | | 0.007 | 0.007 | | 0.006 | 0.006 | |
| Post-intervention period 2 (PIP-2) | 0.008 | 0.011 | 0.012 | 0.008 | 0.008 | 0.009 | 0.007 | 0.007 | 0.008 |
| *Level: Patient:* | | | | | | | | | |
| *Variance / covariance* | Baseline | PIP-1 | PIP-2 | Baseline | PIP-1 | PIP-2 | Baseline | PIP-1 | PIP-2 |
| Baseline | 0.400 | | | 0.400 | | | 0.368 | | |
| Post-intervention period 1 (PIP-1) | 0.367 | 0.508 | | 0.367 | 0.509 | | 0.338 | 0.482 | |
| Post-intervention period 2 (PIP-2) | 0.351 | 0.433 | 0.519 | 0.351 | 0.434 | 0.52 | 0.322 | 0.407 | 0.493 |
| -2Loglikelihood | 31370.1 | | | 31261.1 | | | 30605.6 | | |

* = 0.01 $\leq$ p < 0.05; ** = 0.001 $\leq$ p < 0.01; *** = p < 0.001; s.e. = standard error

shown that the intervention group decreases after the intervention. The estimates in figure 6.2 are based on contrast coding, referring to a female patient who is 65 years old and who does not use psychiatric medication. However, she uses both short-acting hypnotic and short-acting anxiolytic benzodiazepine and belongs to a general practice where the general practitioner did not receive a post graduate course and no reminder letter was sent. Residual diagnostics are checked in all models showing approximate normality.

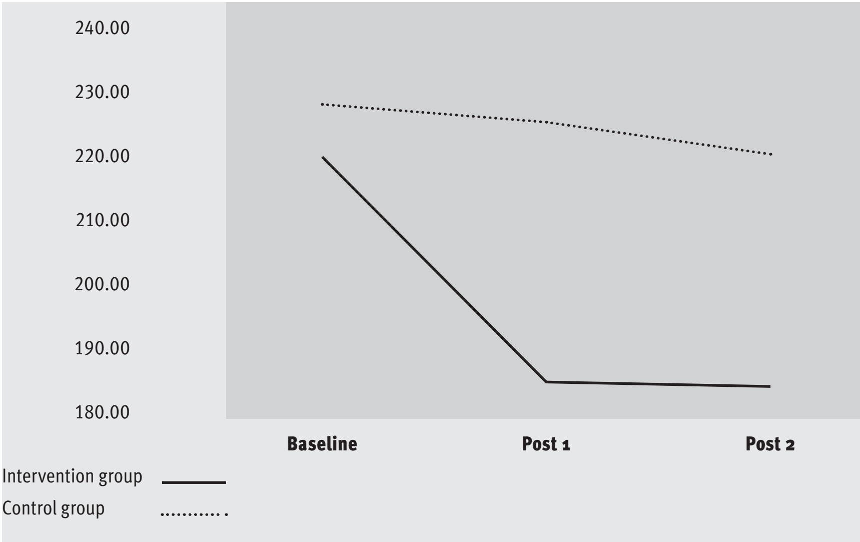
### *6.4 Discussion*

This study demonstrates the reduction of benzodiazepines by means of a multilevel model in a natural field experiment. The reduction is caused by a letter from the general practitioner to his patients. The general practitioners with their patients are allocated either to an intervention group or to a control group. Benzodiazepine use has been the subject of continuing discussion for many years, as well in the primary care setting as in public health policy[1,8,19]. An advantage of the multilevel model is that prescription, patient and general practitioner effects can be analysed simultaneously in a hierarchical structure (Table 6.1) following the plea of Leyland and Goldstein[23]. After adjusting for patient, general practitioner and prescription characteristics the reduction of benzodiazepine prescribing as a result of a letter can be found in the models.
Previous studies have reported this reduction of benzodiazepines by the use of a letter but without using a multilevel model[11,17,18,35]. Oude Voshaar[36] shows that 49% of long-term users remain completely abstinent during two-year follow-up after quitting benzodiazepine use (a discontinuation letter was preceded), while 51% patients relapse after a median period of abstinence of 243 days. By means of multilevel analysis, this study shows that the variability of the general practitioner is small compared to the variability of the patients. This means that the inter-general practitioner variability of the prescription and reduction of benzodiazepines is smaller than the inter-patient variability. Simon[37] found in his study that the variability of the prescription of long term benzodiazepines by general practitioners was significantly greater than expected by chance. An omission in the study of Simon is that patients are not nested within general practitioners in the study design. The result of the current study shows that for reducing benzodiazepine use, we mainly have to concentrate on patient level[38]. Previous studies[9,11,18,35,39] support the reduction of benzodiazepine use by an intervention letter. However Hartlaub[40] argues that the setting of the study could be the reason why he had not found a reduction. To analyse this kind of problems a multilevel setting is prefered.

With the multilevel approach we find that patient age is an significant determinant of benzodiazepine use as confirmed in previous studies[6,11,14,15,20,37,41-46]. Gender is also significant as reported in other studies[13,15,41,47-51]. Many studies[41,48,50,51] mention that women use more benzodiazepines than men. In our study the interaction between gender and age indicates that when people get older, benzodiazepine use is different between men and women.
In this study, short-acting hypnotica is prescribed to 30% of the chronic users.

**Figure 6.2**

**Adjusted benzodiazepine means of model 2, at baseline, post intervention period 1 (Post 1), and post intervention period 2 (Post 2) for intervention and control group**




A decreasing effect can be seen in the use of benzodiazepines for patients who use one drug of two drugs, after adjusting for the other variables. The studies who refer to the effect of short- versus long-acting benzodiazepines[52,53], report that general practitioners tend to prescribe short-acting benzodiazepines. The tendency of prescribing short-acting benzodiazepines is also found in this study. In accordance with the study of Pimlott the proportion of long-acting benzodiazepines decreases more than the combination of short-acting and hypnotics. Adding benzodiazepines to antidepressants is commonly used to treat people with depression. This relation between benzodiazepines and psychiatric medication is not shown in this study, but is reported in other studies[19,37,54,55]. As mentioned before a change can be seen between baseline and pot intervention period 1. The negative correlation (-0.12) between baseline and this change corresponds with the statement of Cormack that after a letter intervention, a high reduction is related with a low baseline drug consumption[9].

*6.4.1 Limitations and strengths*

In this study the information whether the patient actually used the drug is not known, and the indication of the prescription is not taking into account in this study. The patients included this study are only obligatory insured, as about 60% of the Dutch population is obligatory insured with public health insurance funds. Only users of more than 180 DDD are included in the study. Since patients with lower mean baseline drug consumption are more successful at reducing their medication. The strength of this study is the relatively large population size and its realistic practice based design. The benefits of being able to evaluate a large number of patients and doing population-based data-analysis have its definite advantages.

*6.4.2 Clinical Implications*

Improvement in the rational prescribing of benzodiazepines is not achieved by the medical board making new rules but rather by offering general practitioners education in communication and negotiating skills as well as more time with the individual patient who is requesting benzodiazepines[7]. Other possibilities for reducing benzodiazepine prescribing are a leaflet[56], online drug telepharmacy[45] and feedback to general practitioners[57,58].

Another clinical implication is that general practitioners have a tool at their disposal, e.g. sending a letter, to discontinue the use of benzodiazepines. Such a letter is advisable in cases of abuse or heavy use and particularly in the case of elderly.

The findings of the current study are not consistent with those of Pimlot[57] who find that educational material for general practitioners has no impact on general practitioners benzodiazepines prescribing. This paper has outlined a multilevel approach which analyses an intervention study. The study demonstrates that a simple letter from the general practitioner reduces the prescribing of benzodiazepines. Moreover, it will benefit public health.



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## *Appendix A*

The model represents the repeated measures as a multilevel model for three levels. The measurement occasions constitute the first level, the patients the second level, and the general practices the third level. Consequently the data are represented in a format where each record is identified by its measurement occasion t ('level 1 unit'), its patient j ('level 2 unit'), and its general practice k ('level 3 unit').
The fixed and random parts are modelled using dummy variables for the three measurement occasions: baseline (B), post-intervention period 1 (PIP-1), and post-intervention period 2 (PIP-2), defined mutually exclusively so that for each data point exactly one of the three dummy variables is 1. A model with correlated random slopes at level-2 for these dummy variables specifies a fully multivariate model and replaces the level-1 random part[28](p. 174). Omitting the explanatory variables except for the measurement occasions, the expected value for measurement occasion t can be denoted by $\mu_t$ and this model can be expressed by:

$$Y_{tjk} = \mu_t + P_{tjk} + G_{tk},$$

where the fixed part can be written as $\mu_t = \mu_1(B)_{tjk} + \mu_2(PIP\text{-}1)_{tjk} + \mu_3(PIP\text{-}2)_{tjk}$ and does not contain a constant term, but represents the three measurement occasions by three dummy variables.
$P_{tjk}$ and $G_{tk}$ are normally distributed random variables with expectations 0 and variances $\sigma_1^2$ for $P_{tjk}$ and $\tau_1^2$ for $G_{tk}$, and with covariance matrices

$$\text{Level 2: } \mathrm{cov}(P_{tjk}) = \begin{bmatrix} \sigma_1^2 & & \\ \sigma_{12} & \sigma_2^2 & \\ \sigma_{13} & \sigma_{23} & \sigma_3^2 \end{bmatrix};$$

$$\text{Level 3: } \mathrm{cov}(G_{tk}) = \begin{bmatrix} \tau_1^2 & & \\ \tau_{12} & \tau_2^2 & \\ \tau_{13} & \tau_{23} & \tau_3^2 \end{bmatrix}.$$

$\sigma_1^2$ = variance of baseline (B) in level 2.
$\sigma_{12}$ = covariance between level 2 baseline (B) and post-intervention period 1(PIP-1).

The level-2 component of the covariance between B and the difference between B – (PIP-1) is equal to $\sigma_{12} - \sigma_1^2$,
and the correlation between baseline (B) and the change between B and PIP-1 is estimated by: $\dfrac{\sigma_{12} - \sigma_1^2}{\sqrt{\sigma_{dif}^2 \sigma_1^2}}$

where $\sigma_{dif}^2 = \sigma_1^2 - 2\sigma_{12} + \sigma_2^2$

***Appendix B***

*Letter from general practitioner received by intervention group*

Dear Ma'am / Sir,

This letter is directed at you because during the past year, you have regularly received prescriptions for sleep and/or anxiety. Although these medications are generally prescribed to help you through a difficult period, they will not solve your problems in the long-term. You yourself know whether you have benefited from these medications.
It is currently not recommended to take these medications for periods longer than two to six weeks due to adverse side effects. I would like to call your attention to that fact with this letter. If you are willing, I would like to work together with you to decrease or stop your use of these medications.
The most important reasons to stop are the following side effects:

- These medications can be addictive.
- Alcohol increases the effects of these medications and vice versa.
- These medications may make you drowsy and unable to concentrate.

The side effects increase with age. Because of the drowsiness caused by these medications, your chances of falling and possibly breaking bones is increased.
In my opinion, these reasons are sufficient cause to decrease or stop these medications.
A number of people develop symptoms as a result of decreasing or stopping these medications. These symptoms may be similar to those you had before you started the medication. In general, these symptoms will not last long, usually less than two weeks, at which time even people with these symptoms feel a great deal better.
I invite you to make an appointment to come and see me. We can then discuss how best to help you stop these medications. If necessary, we can agree to a gradual decrease in dose.
If you have any other questions resulting from this letter, please do not hesitate to make an appointment.

With kind regards,

Chapter 7

# General Discussion

## *7.1 Introduction*

This dissertation presents four studies using multilevel methodology in the domain of general practice, with a focus on the different methods used. The two common and most important topics addressed by the four studies are the variation between patients and the variation between general practitioners (GPs) – and their interrelation. The combined presence of these two sources of variation is the reason why a nested structure has always been used for the statistical analysis. In the first study (S1) (chapter 2), the global adherence to guidelines was studied for patients who are nested within general practices. In the second study (S2) (chapter 3), the GP workload caused by providing care for patients in socio-economically challenged communities was compared to the GP workload in other communities. In this second study, the patients are nested under their GPs, and they are also nested according to the neighbourhood they live in. In the third study (S3) (chapter 4), we use several measures to investigate which antibiotic prescribing patterns can be distinguished. In this study, antibiotic prescriptions over a period of several years, with repeated measurements for each patient, are nested under the patients. In our last study (S4) (chapter 5), the effect of a letter from the GP to chronic users of benzodiazepines was investigated in an intervention study.
In this study, benzodiazepine prescriptions over a period of several years, again with repeated measurements for each patient, are nested under patients, and the patients were nested under their GPs. Multilevel analysis techniques are effective when looking at the influence caused by different sources of variation such as the patients, the GPs, the neighbourhoods, and repeated measurements.
In the present chapter, we present the main findings of the studies. We will discuss the theoretical and methodological consequences of these results and for future research.



## *7.2 Summary of the four studies*

### *7.2.1 Main findings*

The overall conclusion that gives an answer to the general research question is that both patient and general practitioner characteristics were related to the prescribing of medication. Moreover the multilevel design was applicable to this research question.
The first study demonstrated that the degree of adherence to guidelines was influenced by two practice characteristics (solo or group practice, and rural or urban location) and by all patient characteristics under consideration (age, gender, mean costs, mean volume, and different 'Anatomical Therapeutic Classification'-codes (ATC)). Mean costs, mean volume and different drugs are contact-level costs, volume and drugs, aggregated to the patient over a given time interval. With respect to the characteristics of the general practice, adherence to guidelines proved to be 2% lower in the solo practices than in the other practices. In urban areas it was 2% lower than in rural areas. With regard to patient characteristics, age and gender showed the largest effects. Age showed a negative correlation with adherence, and guideline adherence was 1% lower for men than for women.

**Table 7.1**

**Summary of the four studies**

| | | Study 1 | Study 2 | Study 3 | Study 4 |
|---|---|---|---|---|---|
| **Research method** | | | | | |
| | Descriptive | X | X | X | |
| | Inferential | | | | X |
| | Cross-sectional | X | X | | |
| | Longitudinal | | | X | X |
| | Intervention | | | | X |
| **Nesting structure** | | | | | |
| | General practice | V | | | V |
| | General practitioner /Neighbourhoods | | V | | |
| | Patients | V | V | V | V |
| | Occasions | | | V | V |
| **Number of units** | | | | | |
| | Level 3 | | | | 147 |
| | Level 2 | 190 | RNG-GPs=7 / Menzis-GPs=70 \| Neighbourhoods=29 | 30167 | 8170 |
| | Level 1 | 33432 | RNG=14984 / Menzis=66028 | 5 measurements | 3 measurements |
| Number of records | | 33432 | RNG=14984 / Menzis=66028 | 125707 | 23966 |
| Period | | 1997 | 1997 | 1998-2002 | 1998-2000 |
| Patient: | | | | | |
| Age range | | › 18 yr | › 0 yr | › 18 yr | › 18 yr |
| Mean age (std) | | 43.0 (22.8) | RNG:36.1 (20.7) / RZG:43.3 (22.3) | 44.2 (18.1) | 64.6 (14.97) |
| Women (%) | | 58% | RNG: 53% / RZG: 61.1% | 52.70% | 73.20% |
| Dependent variable | | global adherence | workload | antibiotic prescriptions | DDD benzo prescriptions |

In the second study we found that the GP's workload in socio-economically challenged communities was indeed higher than in other communities. These differences remained when we controlled for demographic characteristics such as age and gender, neighbourhood characteristics, and organizational aspects of the practice. For patients with government funded health insurance, the workload was 7 to 11 percent higher in socio-economically deprived communities. For patients without government funded health care, no difference was found between socio-economically challenged and non-challenged communities. Just as in study 1, the patient variables turned out to be the most important variables in explaining the variance in workload.

In the third study, the variation between patients could be well described by dividing the patients into three groups based on antibiotic prescriptions. The data for the study covered a period of five years. The three groups were: group 1: the non-prescription group, group 2: the varied prescription group, and group 3: the high prescription group. The diagnostic indications for this distinction were derived for each of five diagnostic clusters: 1) respiratory, 2) urinary, 3) dermatological, 4) auditory, and 5) miscellaneous. In these clusters the proportion of patients in prescription group 1 varied from 75% to 95%, in group 2 from 5% to 22%, and in group 3 from 0.5% to 3%. For auditory, there was no high prescription group. Age was positively correlated to the amount of antibiotics prescribed.

In study 4 we found that the informative letter from the GP to chronic benzodiazepine users advising them to reduce or cease using benzodiazepines was effective. We concluded this as there were fewer benzodiazepine prescriptions written following the intervention. The reduction of prescribing was 16% after a half year, and 14% after one year. Not taking the covariances into account, the explained variance on general practitioner level, was 22 % before intervention, 44% a half year after the intervention , and 37% one year after the intervention. At patient level the explained variances were respectively 8%, 5% and 5%. Taking the covariances into account, the explained variances on general practitioner level for the three periods: baseline, post intervention period 1 and post intervention period 2 were respectively 25%, 27% and 28%. At patient level the explained variances were respectively 8%, 7% and 7%.

*7.2.2 Characteristics of the studies*

In table 7.1 a summary of the four studies is given classified according to research methods, nesting structure, total units by level, total number of records, time period of the research, demographic characteristics of the patients, and dependent variables. The recruitment will also be discussed.

With regard to research methods, the studies were classified according to two principles: a) exploratory versus testing and b) longitudinal versus cross-sectional. Three of the studies are exploratory (S1, S2, and S3) while the fourth study (S4) focuses on hypothesis testing; two studies are longitudinal (S3 and S4) and two are cross-sectional (S1 and S2).

Table 7.1 also shows the organization of the four studies with respect to the nesting structure or multilevel structure. The following levels are distinguished: general practices, GPs, neighbourhoods, patients, and repeated measurements (for the

patients). As patient variation is the most important focus for all of the studies, it is represented in all of the studies.
Studies S3 and S4 are longitudinal and present repeated measurements nested under patients. In study 2 (S2), the patients are nested under the GPs as well as in neighbourhoods, which leads to a cross-classified model. The model is cross-classified because GPs and neighbourhoods are present in different combinations, which makes case nesting impossible. Combining all this, we can distinguish a total of five levels: repeated measurements (level 1), nested under patients (level 2), nested under GPs (level 3), who are nested within general practices (level 4), while the general practices are cross-classified with the neighbourhoods (level 5). In two studies (S1 and S2) the GP data concerning the nesting structure was not available, therefore the data were aggregated to the general practice level.
Table 7.1 shows the total units per level, including the number of patients, the number of GPs and/or the number of general practices. The number of patients in these four studies ranges from 8,170 to 66,028. The number of GPs ranges from 7 to 70, and the numbers of general practices ranges from 147 to 190.
The total number of records varied from 14,984 to 125,707.
The period wherein the data were collected is from 1997 to 2002.
The demographic characteristics, age and gender are presented in table 7.1 to present an overview of the demographic distribution between the studies. In three studies (S1, S3, S4), patients under age 18 were excluded. The mean patient characteristics (age and gender) in study 4 are different from the other studies, because the average age of chronic benzodiazepine users is higher than the norm. Study 4 showed a mean age of 65 (SD 15) with 73% women. In the three other studies (S1, S2, and S3), the mean age is from 36 to 44 years. The percentage of women is more than 50% in all four studies.
The dependent variables are all related to prescribing. The global adherence was defined as prescribing of a drug which is mentioned in the Groningen Formulary[1]. The workload of the GP was calculated by taking into account: 1) the number of contacts with the patient; 2) the number of care episodes per patient; 3) the number of prescriptions per patient. The total number of antibiotic prescriptions per year per patient was used as the dependent variable in study 3, and in study 4 the sum of the defined daily doses of benzodiazepine prescriptions in per six-month-period per patient was used as the dependent variable.
The data for the four studies were recruited from the insurance company MENZIS (S1 and S4) and from the Morbidity and Medication Registration Network Groningen (RNG) of the Department of General Practice at the University Medical Center in Groningen (UMCG). In study 2, data from the RNG as well as data from MENZIS are used. A common characteristic of all studies is that the data originate from databases designed for administrative purposes. The data from the RNG are also used for patient care. The RNG data are reliable, because the GPs were intensively trained and they received feedback about the data they provided between four and six times per year[2]. All of the assistants and researchers who were involved in this data processing meet regularly. The GPs who are involved in the RNG are not a random sample selected from the Dutch GP population. However, the GPs of the RNG are comparable with their regional colleagues based on information from the regional health care organizations. With respect to incidence and prevalence, the morbidity pattern seen in the RNG data does

not deviate significantly from other GP registration groups. Administrative databases have been criticized for underestimating the prevalence of certain diseases (co-morbidities). However, Maselli et al. concluded that administrative databases are accurate sources for measuring profiling[3]. In her study, Lamers presents a comparison between a pharmacy database and a database from a general practice. She ascertains that the only objection to use a pharmacy database is the absence of diagnoses[4]. Treweek mentions that we have to make careful interpretations when using data generated by GPs. She concludes that data from GP generated databases may support quality improvement work, however this requires an awareness of how the electronic medical record system is actually used by general practice staff[5]. As previously mentioned, the data are primarily registered for administrative purposes. But if attention is paid to consistent registration in a standardized way, and if this is supported by regular meetings and feedback, the general practitioner registration system can be used for the evaluation of the GPs' activities and professional competencies, as is also demonstrated in this dissertation. The general practice registration system can be used for other purposes such as education. Additionally, policy decisions may be based on the collected data, such as is seen when looking at the workload of GPs in socio-economically challenged communities.



#### *7.2.3 Limitations*
We used pre-existing data for these studies, and therefore we had to make use of existing patient, GP, and general practice variables. This implies that we could not develop operationally well founded variables in an optimal way. The patient variables appeared to be related to medical variation, but the higher-level variables, such as the GP and practice variables, showed a weak relationship to medical variation. This may be due, in part, to the fact that we were limited to the existing variables, and that no other variables could be used other than those previously collected in the databases. It would be interesting to collect additional relevant variables at both the GP and practice level, this allowing to explain more of the variance in the outcome measures under study. Additional GP-level variables are for example: collaboration with (Farmaco Therapie Overleg) FTO-group and connected with family practice research networks. An example of an additional variable at practice level is the availability of other paramedical specialisms.

### *7.3 Methodological issues / reflections*

#### *7.3.1 Methodological issues*
In multilevel research, the data structure in the population is hierarchically nested (in this case, patients nested in a general practice), and the data are regarded as a multistage sample from a hierarchically structured population. In such samples, the patients in the same practice, or with the same GP, are generally not independent because they are treated in the same organization or by the same person, because of selection processes, and due to the common context and history they share as a result of belonging to the same general practice.

Table 7.2

**Overview of independent, dependent and stratification variables of the different studies grouped by level**

| | | | |
|---|---|---|---|
| **Level 4:** | **Level: General Practice** | | **Stratification variables:** |
| Characteristics: | 1. Mean age of the GPs | | |
| | 2. % men of the GPs | | |
| | 3. Mean male patients | | |
| | 4. Mean female patients | | |
| | 5. Practice-type | | |
| | 6. Location of the practice | | |
| | 7. Allocation | | |
| | 8. Intervention | | |
| | 9. Education group | | |
| | 10. Reminder letter | | |
| **Level 3:** | General practitioner | Neighbourhood | Insurance: |
| Characteristics: | 1. Organisation | 1. Deprived area | 1. Public |
| | | 2. Percentage of foreigners | 2. Private |
| **Level 2:** | Patient | | Diagnosis group: |
| Characteristics: | 1. Age | | 1. Respiratory system |
| | 2. Gender | | 2. Urinary system |
| | 3. Insurance | | 3. Dermatological system |
| | 4. Duration in practice | | 4. Auditory system |
| | 5. Aggregated mean Costs | | 5. Miscellaneous-group |
| | 6. Aggregated mean Volume | | |
| | 7. Aggregated different ATC-codes | | |
| Dependent variables: | | | |
| Adherence: | Global adherence | | |
| Workload: | 1. Vis-à-vis contacts | | |
| | 2. Episodes | | |
| | 3. Prescriptions | | |
| **Level 1:** | Intra-patient | | |
| Characteristics: | 1. Occasions | | |
| Dependent variables: | | | |
| Prescription: | 1. DDD’s of benzodiazepine | | |
| | 2. Antibiotic prescriptions | | |



1 There are two main general arguments for applying a multilevel design. The nature of the research question, in which various units of analysis play different roles, such as patients and GPs. Because the dependent variable is always a micro-level variable, usually one or more variables defined at a higher level (so-called macro-level variables) will be included among the independent variables. Methodologically the presence of macro-level variables is, however, not a requirement.

**Table 7.3**

**Intra class correlations from patients nested-studies**

| Study | N-patients | N-GPs | N-Ward | Age mean (std) | % Female | Dependent. variable | Proportion macro-level | ICC‡ |
|---|---|---|---|---|---|---|---|---|
| Sixma_1998 | 7659 | 152 | | 41.9 (17.5) | 47.8 | | | |
| | | | | | | Access | 0.099 | 9.9 |
| | | | | | | Humaneness | 0.077 | 7.7 |
| | | | | | | Information | 0.053 | 5.3 |
| Bolanos-Carmona_2002 | 52152 | 38 | | | | Visits | 0.061 | 6.1 |
| | | | | | | Referrals | 0.040 | 4.0 |
| | | | | | | Diagnostic tests | 0.066 | 6.6 |
| Veenstra_2003 | 3714 | | 67 | 63.0 (16.0) | 54 | PEQ* | 0.013 | 1.3 |
| Zantinge_2007 | 1160-2095 | 140-142 | | 43 (22.0) | | Psych. Problems | 0.09 | 9 |
| | | | | | | % eye contact | 0.19 | 19 |
| | | | | | | Empathy | 0.09 | 9 |
| | | | | | | Psychol/social | 0.08 | 8 |
| | | | | | | Pat-centeredness | 0.13 | 13 |

* PEQ = Patient Experiences Questionnaire‡ ICC = Intra class correlation

2 The mutual dependence of observations, inherent to a nested data structure, renders invalid more common research methods, which require independence of cases.

Each of the four studies satisfies both arguments, as may be concluded from the substantive importance of the levels as mentioned in tables 7.1 and 7.2.

*7.3.2 Number of units needed per level for a multilevel analysis*

Multilevel design is being applied increasingly to nested data structures. There are different opinions regarding the minimum number of units needed, on the macro as well as on the micro level[6-9]. A number of authors standardly use a minimum of 100 to 150 subjects[8], or a rate of 5 to 10 subjects per variable when applying a single-level statistical model[10]. The efficiency and power of multilevel tests is based on pooled data of units at two or more levels, which requires large datasets. Kreft's simulation study[6] showed that adequate statistical power is achieved with at least 30 groups of 30 observations each, 60 groups of 25 observations per group, or 150 groups of 5 observations per group. The number of groups has a stronger effect on the power than the total number of observations, although both are important. The numbers that are used in our four studies are sufficient with the partial exception of study 2, for which only seven GPs were present at the macro level for the RNG section of the study. These results are therefore purely exploratory with respect to the GP level.



Theoretically, a total of five levels may be distinguished in the four studies. If we put all the variables from the four studies together in one design and require strict nesting, we can reduce the number of levels to four. In table 7.2 a summary of the dependent and independent variables is presented, indicating the stratification variables. The interaction terms are not included in this summary.

A basic operation when using a model with several levels is to decompose the total variance across the levels. This allows us to compute several kinds of intraclass correlations, indicating the relative variance contribution of individual levels. For example, we can find out the proportion of total variance accounted for by the GP. In two studies (S1 and S4) it was not possible to nest the individual GPs within general practices, therefore the data were aggregated to the general practice level. As a result, it was impossible to make a distinction between 'general practice variation' and 'general practitioner variation'. The intraclass correlations are summarized and discussed in Section 7.3.3.

*7.3.3 Reflections with regard to the methodology*

In addition to the reasons previously mentioned, the size of the intraclass correlation (ICC) may be important when deciding whether or not to apply a multilevel design. This coefficient indicates the contribution of the higher level to the variation in the outcomes of the dependent variable(s). In table 7.3 the ICCs found in some multilevel studies reported in the literature[11-14] are presented, to give an impression of the amount of ICC in different studies of general practice. In this literature the ICCs for two level cross-sectional designs in which patients are nested under GPs, vary between 1.3 – 19%.

The ICCs (i,e., proportions of variance at the practice or GP level) in all four studies are very low when compared to the other studies in table 7.4, with the exception of

**Table 7.4**

**Variance partition coefficients of the four studies**

| | | | Neighbourhood | General Practice | General Practitioner | Patient | Intra-patient |
|---|---|---|---|---|---|---|---|
| **Study 1** | | | | 0.02 | | 0.98 | |
| **Study 2** | | | | | | | |
| RNG | Vis-a-vis | | | | | | |
| | | ZF0 | 0.01 | | 0.004 | 0.99 | |
| | | ZF1 | 0.03 | | 0.005 | 0.96 | |
| | Episodes | | | | | | |
| | | ZF0 | 0.02 | | 0.02 | 0.96 | |
| | | ZF1 | 0.03 | | 0.03 | 0.93 | |
| | Prescriptions | ZF0 | 0.03 | | 0.008 | 0.96 | |
| | | ZF1 | 0.04 | | 0.03 | 0.93 | |
| RZG | | ZF1 | 0.02 | | 0.01 | 0.96 | |
| **Study 3** | | | | | | | |
| | Number of antibiotic prescriptions of the body-system: | | | | | | |
| | Respiratory | | | | | 0.84 | 0.16 |
| | Urinary | | | | | 0.94 | 0.06 |
| | Skin | | | | | 0.97 | 0.03 |
| | Auditory | | | | | 0.97 | 0.03 |
| | Miscellaneous | | | | | 0.93 | 0.07 |
| **Study 4** | | | | | | | |
| | DDD's of Benzodiazepine | | | 0.02 | | 0.78 | 0.20 |



study 4 and the cluster respiratory-body system of study 3. In study 2, if we would ignore the neighbourhood level, the associated variance would be added to the variance at the general practice level, yielding intraclass correlations from 0.013 to 0.07. In chapters 2 (S1) and 3 (S2), a multilevel design is used in which the patient level is the lowest level. Based on both studies, we conclude that the patient level has a larger variance partition coefficient than is found at the GP level. In chapter 2 (S1), it appears that 98% of the total variance of the global adherence is accounted for at the patient level.

Concerning the GP level, studies 1 and 4 did not include the GP level in the study design (table 7.1). In order to assure anonymity in these studies, the data were not released at GP level, but aggregated to the level of the general practice. Moreover, in certain duo-practices it was not possible to make a distinction between the GPs of the patients. This means that the GP level was skipped, and two levels remained. According to the study of de Jong[15], the loss of information resulting from this aggregation is minimal. De Jong[15] found more similarities between GPs who share a work environment than between GPs who do not share a work environment. These similarities[15] consist primarily of self reported behaviour, and

behaviour reported by the GP during GP-patient contact. De Jong[15] concluded that variation seen at the practice level does not only indicate individual differences in the GPs, but also patterns that are formed by social processes caused by the interaction between the GP and local circumstances. This suggests that there is not a large loss of information in studies 1 and 4 due to aggregation to the practice level.
Table 7.4 shows the variance partition coefficients for the four studies. The largest proportion of variance is found at the patient level (range: 0.78 – 0.99). The cross-sectional studies (S1 and S2) show higher coefficients at the patient level than the longitudinal studies. In the longitudinal studies, 3 to 20 percent of the variance is found at the intra-patient level. Study 2 includes a comparison between patients on government funded health care (ZF1) and privately insured patients (ZF0). This shows that there is less patient level variance in the ZF1 group, which is why the contextual variance is proportionately larger in this group.



Two studies in this thesis presented multilevel models of a special nature. In chapter 5 (S4) a repeated measurement design was used with the defined daily dose (DDD) of prescribed benzodiazepines as the dependent variable. The three sources of variation were the repeated measurements, the patients, and the general practice. This design can be modelled as a multilevel structure. These repeated measurements, in this case three in number, are the first level in multilevel terminology. The three measurements include one at baseline, one at post intervention period 1, and one at post intervention period 2. The measurements are nested under the patients (the second level), and the patients are nested under the general practices (the third level). The basic version of the multilevel model that could be used, in this case a three level random intercept model, implies equal variances for all three measurements and equal correlations between all pairs of measurements, which means a severe restriction for the statistical model. If no independent variables are included in the three-level random intercept model, four parameters can be distinguished: one parameter that represents the mean DDD of the prescribed benzodiazepines and variance parameters for each of the three levels. This model will further be referred to as model RM0. In this model the repeated measurements are not included in the fixed part of the model. If these measurements are included as a linear variable (time), the model is extended with five extra parameters, one parameter for the fixed part of the model representing average differences between the measurements and two random slopes of the variable time, indicating differential variability in trends over time between, respectively, practices and patients; with two associated slope-intercept covariance parameters. These two random slopes are parameters for the general practice level and the patient level, respectively. We call this model RM1. The time variable here is assumed to have a linear effect, in which the change per unit of time is constant for each patient but allowed to differ between patients and between GPs. This assumption can also be stated by saying that the difference between post intervention period 1 and baseline is the same as the difference between post intervention period 2 and post intervention period 1. In a further extension of this model, the assumption that time has a linear effect is dropped. This leads to model RM2. For each of these models the restriction of equal variances within patients for all three measurements, and equal

**Table 7.5**

**Comparison between models by deviance (-2LL), Akaike Information criterion (AIC), Bayesian Information criterion (BIC), and their differences express in Chi-square and degree of freedom difference (df_delta)**

| | | Models | | | | | |
|---|---|---|---|---|---|---|---|
| | | RM0 | RM1 | RM2 | FM0 | RM-fin | FM-fin |
| | -2LL | 32266 | 31571 | 32142 | 31370 | 30856 | 30606 |
| | K | 4 | 9 | 7 | 15 | 31 | 39 |
| | AIC | 32274 | 31589 | 32156 | 31400 | 30918 | 30684 |
| | BIC | 32307 | 31662 | 32213 | 31521 | 31169 | 30999 |
| | | df_delta | | | | | |
| | RM0 | - | 5 | 3 | 11 | | |
| | RM1 | 695* | - | 2 | 6 | | |
| Chi-square | RM2 | 124* | 571* | - | 8 | | |
| | FM0 | 896* | 201* | 772* | - | | |
| | RM-fin | | | | | - | 8 |
| | FM-fin | | | | | 250* | - |

* = $p<0.001$; K = number of parameters; fin = final; -2LL = minus twice the natural logarithm of the likelihood; RMx (where x =0, 1, 2, fin) = repeated measurement model x; FMx (where x = 0, fin) = fully multivariate model x

correlations between all pairs of measurements, still remains. The assumption of the validity of such restrictions can lead to incorrect conclusions if they are not valid in practice, especially in large datasets such as the ones in our four studies. Therefore, we chose in this study (S4) for a so-called fully multivariate model (FM0). In the fully multivariate model, the expected values and the covariance matrix are estimated without any restrictions, so that restrictions of equal variances and equal correlations are not made. According to Snijders[9], one of the characteristics of the fully multivariate model is that in the case of a balanced dataset, the fully multivariate model corresponds to the usual multivariate analysis of variance (MANOVA) model, and the estimates of means, regression coefficients, variances and covariances will be the same. Each of the other multilevel models mentioned is a submodel of the fully multivariate model. To compare the previous models (RM0, RM1, RM2, FM0) we calculated the deviances and two associated goodness of fit indices (GOF): Akaike's Information criterion (AIC) and the Bayesian Information criterion (BIC). In table 7.5, the GOFs of the models are presented and the differences in deviances are calculated (omitting meaningless comparisons). Table 7.5 also includes the two final models, RM-fin and FM-fin. These are models in which independent variables have been added, and which are similar to the RM and FM models with respect to the restriction of variances and correlations. Model FM-fin is the final model as it is included in study 4 (chapter 5). Model RM-fin is an extension of RM0 with variables that appear in this final model. Comparing the models RM0, RM1, RM2, and FM0 with each other, it appears that the null model (FM0) of the fully multivariate model is the best with regard to the two GOFs. Based on this result we can expect that the final model of the fully multivariate model will be the best (AIC = 30684; BIC = 30999). Comparing the two final models RM-fin and FM-fin confirms this same result.

#### *7.3.4 Latent class*

A variant of the multilevel model, namely a multilevel latent class model, is applied in chapter 4 (Study S3). This model is used to investigate antibiotic prescribing patterns in general practices over a period of five years. The longitudinal character of the data was taken into account by the specification of the latent class model. The usual assumption for multilevel models with longitudinal data is that the differences between the individuals are normally distributed. A different possibility is to make the assumption that the individuals differ in the sense that they belong to different discrete groups. These groups are called latent classes, because they are not directly observed but have to be estimated from the data. Such models have been proposed by Vermunt[16,17], generalizing previous models developed by Lazarsfeld and Goodman. In chapter 4, the patients are clustered in groups (forming latent classes) that are homogeneous with respect to the amount of antibiotics prescribed. For these kinds of medication variables, which develop over a period of several years, a model with latent classes is more suitable than a model with normal distributions. The reason is that discrete latent classes, because of their flexibility, are better for representing the discrete and skewed distributions typical of prescription data. An additional level of detail is possible because for each prescription in this data set, the prescribed antibiotic is known. The latent class structure can thus differ according to the indication cluster, or system. A two-class solution was found as the best interpretable solution for the auditory system, while for the other indication clusters, a three class solution worked best. These three classes may be described as group 1: the non-prescription group, group 2: the varied prescription group, and group 3: the high prescription group. These names reflect the ordering of the classes with regard to the number of prescriptions. To a good approximation, the average number of prescriptions in these groups was constant over the five years of this study. The fact that such a latent class solution provided a good representation of the data points towards a high degree of continuity over time in the extent of antibiotic prescribing per patient. In order to assess the validity[18] of these solutions, the relationship was calculated using known variables, in this case: age, gender, and the insurance status of the patient. Relationships found by other investigators[19-21] with regard to antibiotic prescribing were confirmed in our study. If more variables had been measured, it would be possible to relate these classes to other patient variables, allowing further use of this type of analysis. Classes 2 and 3 are the most important ones relating to the GP in view of the risk of developing antibiotic resistance.



### *7.4 Contextual and compositional effects*

The use of multilevel modelling is the only statistically viable way to distinguish compositional from contextual effects[22]. In chapter 4 (study 2), a distinction was made between contextual and compositional effects. Goldstein and Leyland[23] discussed these effects as follows: The questions facing researchers concern the degree to which observed differences at the macrolevel – typically GPs or general practices – reflect genuine contextual differences between those general practices, or whether they do little more than reflect the composition of those general practices in terms of microlevel (here: patient-level) factors. In accordance with Duncan[24] the two types of effects can be described as follows: The composition of the general practice in chapter 4 refers to the make-up of the general practice in terms of the net characteristics of the patients who attend the general practice (for example foreigners); the contextual differences are the additional differences between general practices, that cannot be attributed to differences in the composition[23]. In addition to these two effects, Duncan distinguishes a third aspect, namely the interaction between composition and context. Similar to Goldstein and Leyland, we consider compositional variables at the micro as well as at the macro level.

In order to demonstrate the distinction between compositional and contextual effects, we can use the results presented in table 4.4 of chapter 4, limited to the number of prescriptions for patients who have government funded health care as the dependent variable.

We consider the coefficients of the two following variables: percentage of foreigners as a compositional effect, and whether or not patients live in a socio-economically challenged neighbourhood as a contextual effect. Figures 7.1a and 7.1b show the relationship between the mean number of prescriptions for government funded patients (y-axis) and the percentage of foreigners in a neighbourhood (x-axis). The relationship is represented by a dashed line for patients living in a socio-economically challenged neighbourhood and by a solid line for patients in other neighbourhoods, controlled for the remaining variables. The percentage of foreigners represents the compositional effect of the neighbourhood. With respect to the contextual effect, which is expressed as the difference between socio-economically challenged and non socio-economically challenged communities, the number of prescriptions was 7% higher in socio-economically challenged communities.



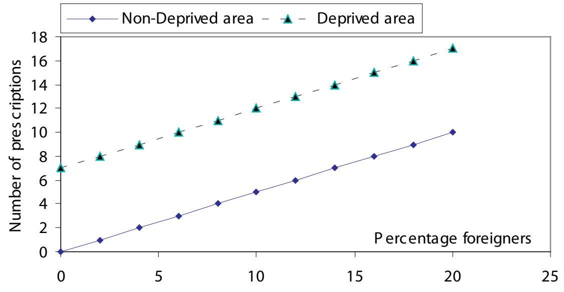
Figure 7.1b shows that, when the percentage of foreigners is low, there is only a small difference in the number of prescriptions between socio-economically challenged and non-challenged neighbourhoods. The difference becomes larger when the percentage of foreigners increases in such a way that the effect of the percentage of foreigners in a socio-economically challenged neigbourhood increases steeper than in other neigbourhoods. Duncan[24]. noted that the distinction between contextual and compositional effects is generally relevant, and that these concepts are applicable not only in cases where the attention is focused on the context, i.e. neighbourhoods, but also if the context can be seen in terms of administrative units (i.e. group practices), time periods, or institutional settings. Van Weel[25] argues that besides the neighbourhood in which the patient lives, the patient's family and work situation should also be considered as context. The patient's family, work situation, and neighbourhood all belong to the background setting in which the patient's health problems take place. It is this context in particular which determines the complexity of the GP's role.

### *7.5 General conclusions*

The theoretical and methodological aspects involved in modelling the variation found in a medical practice are continually developing[26], and the application of

**Figuur 7.1a**

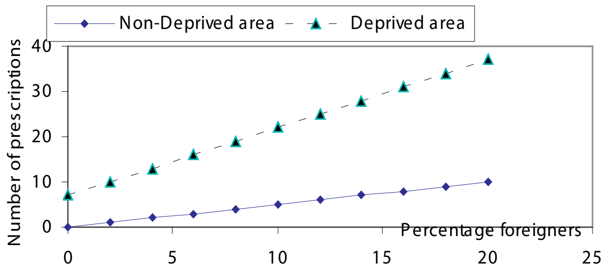
**The relation between number of prescriptions and percentage of foreigners (no interaction)**




**Figuur 7.1b**

**The relation between number of prescriptions and percentage of foreigners (interaction)**






multilevel models represents a major step forward. The studies in this thesis show that patient characteristics are more important than the characteristics of either the GP or the general practice, when modelling the medical variation in general practice using a minimal multilevel design (a design with the patients nested under GPs). This agrees with other sociological research in which multilevel analysis was applied. Because of the importance of not only patients but also GPs and practices on processes and outcomes in primary care, multilevel analysis is the only reliable way to estimate and test the effects of GP characteristics and case-mix characteristics on patient level outcome variables. For an explanation of the variance in patient-level-variables in a general practice, the variables at the patient level are usually the most important. In this thesis, the patient's age turned out to be the most important of the case-mix variables. Age is negatively correlated to adherence to guidelines and the prescribing of benzodiazepines, while there is a positive association with antibiotic prescribing and GP workload (the number of face to face contacts, disease episodes, and prescriptions).
With respect to the variables at the level of the GP and the medical practice, the practice type (single or group practice) shows an important relationship with the medical variation, while the designation of a community being socio-economically challenged does not show a clear association with medical variation in these studies.
Moreover, multilevel research methodology can be used in the context of quality

of care research, and in particular in relation to indicators of quality of care, also called performance indicators. Performance indicators are used as a tool in quality improvement as well as in performance-based reimbursement programs that reward health care providers for meeting preset targets[27,28]. Reliable and valid measurement of quality is essential. One of the problems in measuring quality of care provided by a particular health care provider is the issue of differences in case mix of the patient population underlying the performance. Multilevel research methodology can provide here an important progress[29,30] by assessing the relative contributions of different levels or types of providers (e.g. GPs, GP-groups) and patients to the performance measured, such as prescribing.
Also in the domain of care in deprived areas (described in study 2), the Ministry of Health Wellness and Sports (VWS) and the health insurance companies set up a fund (Achterstands Ondersteunings Fonds). This led to an administrative intervention for improving the quality of care that patients living in disadvantaged communities in large urban centres, receive. From this fund, financial incentives were offered to achieve assigned-quality-related performance targets. The underlying assumption is that the incentives will motivate providers to achieve the performance targets. Multilevel research helps to clarify the causes and associated interventions for poor performance. For example, GP-level variation of global adherence may be indicative of differences in clinical training among GPs, pointing to a need for the implementation of evidence-based guidelines. However the greatest proportion of observed variation was actually at the patient level, which raises a question about what might be gained by directing incentives to patients to modify their own behaviour[31]. Research that determines the contribution of each provider level to observed variation in care, can inform policy decisions regarding incentives. If policymakers and insurers can better understand the sources of variations in performance, they will be more able to develop payment systems that reward providers based on the quality of care[32].
Choosing to look at compositional or contextual variables depends largely on the research question[33]. This implies that in the case of medical variation, it is impossible to indicate unambiguously in a general way whether medical variation is primarily related to the composition or the context.



For the specific studies the most important conclusions may be summarized as follows:
With respect to the medical variation represented as adherence to guidelines, it appeared that adherence is lower for older patients and for men, and also it is lower in solo practices compared to group practices, and in urban compared to rural regions; among these, the patient characteristics are more important than the practice characteristics (S1).
With respect to the medical variation represented by the GP workload, in the case of patients with government funded health care, we found that there was a difference depending on whether or not they lived in a socio-economically challenged neighbourhood. This difference was not found for patients with private medical insurance. In this study again, the patient characteristics were the most important predictors.
With respect to the medical variation seen in antibiotic prescribing, a distinction of patients in three groups appeared to be empirically meaningful: 1) the largest

group, in which no antibiotics were prescribed, 2) a smaller group, in which a varied pattern of prescribing was seen, and 3) the smallest group, in which antibiotics were prescribed on a regular basis. In this study it made more sense to divide the patients into three categories than considering them as a single group distinguished by continuously varying differences. The patient characteristics (age and gender) are related to these three groups (S3).
With respect to the medical variation represented by benzodiazepine prescribing, it appeared that a written recommendation by GPs to chronic benzodiazepine users, advising them to decrease benzodiazepine use, leads to a reduction in benzodiazepine prescriptions for these patients (S4).

The development of multilevel analysis started in the 1980s and became widely accepted among methodologists in the 1990s, but there are still many researchers who are somewhat reluctant to apply it. The studies in this thesis illustrate that multilevel analysis has many advantages compared to analysis at a single level. Single level analyses at either the GP or patient level carry the risk of leading to incorrect or incomplete conclusions. The complexity of multilevel techniques does not need to prevent their use, as we have demonstrated in this dissertation. In fact, the flexibility of the model should be a stimulus for researchers to apply multilevel analysis more frequently. In addition, graphic representation of the multilevel models can be helpful for their development and testing.



In this study the intraclass correlations seen in the structure with patients nested under GPs, general practices, or neighbourhoods, were very low. This could be regarded as an argument for using a single level model instead of a multilevel model. One would, in that case, choose the patient level because most of the variance is present at that level. Whether this is warranted depends in the first place on the effect this would have on the significance level of hypothesis tests. The consequence of ignoring the multilevel structure can be summarized by saying that treating a two-level design as a single-level design will inflate t-statistics erroneously by a factor which is approximately the square root of the design effect. The design effect is a measure combining the size of the clusters or groups and the intraclass correlation[9]. For a design effect less than 1.2 the inflation of the $t$-statistic, and the associated unjustified lowering of the $p$-value, are so small that they are not very serious. For higher values of the design effect, however, ignoring the multilevel structure has undesirable consequences. Because of the large number of patients in each general practice the design effect is larger than the threshold value of 1.2. Notwithstanding the relatively low values we found for the intraclass correlations or variance partition coefficients at the GP level, multilevel analysis remains the model of choice because the importance of the GP level variance is multiplied by each GP's number of patients.

### *7.5.1 Implications*

The implications for directions of future medical research will be discussed separately for each study.
In study 1, we investigated the global adherence to medical guidelines. Apart from the global adherence, Kamps also distinguished the specific adherence. As multilevel methodology has been applied in this dissertation, with regard

to global adherence, it could be useful to investigate the specific adherence in a multilevel design.
In study 2, we demonstrated that the GP workload shows a weak relationship with the way the general practice is organized. Solo practices are expected to merge increasingly with larger professional organization forms such as group practices and health centres. This will necessitate further studies into the workload and the quality of care in these newly developing professional organizations. The nature of these organizations, consisting of groups of GPs, implies that here again, multilevel techniques – distinguishing between patients, doctors and other professionals, and practices – will be the most suitable method to analyze clinical activities[26].
In study 3, we suggested that with regard to the three antibiotic prescription groups (no prescriptions, various prescriptions, and many prescriptions), the second, intermediate group, turns out to be the most important group when considering the development of antibiotic resistance. With respect to this group, the GP would be able to coordinate medical policies to limit antibiotic use, thereby preventing patients from becoming chronic users. It turns out that the closeness between patient and GP can be investigated by evaluating an intervention, such as preventing patients to become chronic users of antibiotics.
In study 4, we found that a letter from the GP recommending the reduction or cessation of benzodiazepine use resulted in decreased use. Based on this empirical result, it would be interesting to carry out further research to investigate patients' reactions to letters about other specific medications and medical issues and to explore additional forms of non-conventional communication methods between GPs and their patients.



As this dissertation is primarily methodologically oriented, it will hopefully stimulate an increased use of multilevel analysis techniques in the research of general practice issues. The development of latent class models (an extension of multilevel analysis) presents perspectives well adapted for research involving variables with discrete or skewed distributions. However, besides methods, theories are also important for scientific advancement. For a theoretical argumentation of research involving medical variation, the supplier-induced demand theory[34,35], the income incentives model[32], or the demand control model[36] (with regard to workload) are good starting points. But these theories are not sufficiently specific, and there is an urgent need for these and other general theories and models to be further elaborated for this particular research domain, and to take into account the specific nested position of patients, GPs, and practices. Such theories would be a major help in starting to explain which variables, GP dependent or practice dependent, are responsible for the variation seen between GPs and between practices.

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# Summary

***This dissertation applies multilevel analysis to large databases originating from general practices. The multilevel aspect concerns the way the data of patients and general practitioners (GPs) are taken together in one analysis, viz. patients nested within GPs. The reason for this dissertation, and the layout are described in chapter 1.***

Chapter 2 includes a description of multilevel methodology, in which case the research question and the data structure, as used in research with regard to the general practice, is important. As well the research question as the data structure refer to two populations, patients and GPs. In a statistical sense, the concept 'dependency' is crucial: because the observations of patients are nested within GPs, there is a dependency between the data of patients of the same GP. Because of this, the traditional analysis methods, as linear regression-analysis, that are based on the assumption of independent observations, are not directly applicable. This is explained in chapter 2, in which case the arguments for the choice of multilevel modelling are given, such as the decomposition of different variance components, the calculation of random slopes, or the fact that multilevel models need less assumptions in comparison with the classical ANOVA-models. Finally, in this chapter, the advantages of the use of multilevel modelling will be discussed. The chapter ends with the main research question. In the multilevel-analysis results of GPs or general practices are adjusted with factors that characterise the patient population of the GP or the general practice (case-mix) as diagnosis, age and gender.



This research question concerns four choice-topics with regard to prescribing. The issue of the four choice-topics concerns:

1 The relation between prescribed and adherence to guidelines
2 The relation between workload of the GP and the patient and his neighborhood
3 To map out the prescribing of antibiotics, taking into consideration the diagnostic variation
4 The reduction of benzodiazepine prescribing in an intervention study

In chapter 3 the term 'global compliance' is used to describe the variance of patients nested within GP-practices in a two level model. Global compliance is defined as the prescribing of a medicine that is mentioned in a formulary. This chapter investigates the extent to which global compliance can be explained by patient and GP-characteristics. For 269067 patients of 190 general practices in the North of the Netherlands, the global compliance was defined as the outcome measure in a two-level model. The mean global compliance was 82%. Two general practices variables viz. organisation of the practice and the degree of urbanisation were related to the global compliance. The patient characteristics that are related to the global compliance are the case-mix variables age and gender, and variables that are aggregated from prescription to patient level, viz. costs, volume and different Anatomical Therapeutic Chemical-codes (ATC). The total explained variance of the final model in which GP-practice variables, patient characteristics and variables that are aggregated to patient level, turned out to be 28%.

In chapter 4 the workload of the GP is investigated using a model in which the patients are nested within GPs and the patients are also nested within a neighborhood (postcode-area). This model is called a cross-classified model. By means of this model the question on whether the workload of GPs working in deprived areas in Groningen is higher than in non-deprived areas. The workload was operationalized by means of the total number of prescriptions, the total number of face-to-face contacts and the total number of episodes. The data derive from the Registration Network Groningen (RNG) and the biggest regional health insurance company. The data from this insurance company include the prescription data of 66028 sickfund-patients enrolled in the practices of 70 GPs. Concerning the RNG, 14984 patients (54.2% being sickfund patients) were enrolled in the practices of 7 GPs. They are stratified by insurance type. The conclusion was that the workload turned out to be higher in the deprived areas. The most important determinants of the workload were patient-characteristics. Among the patient-characteristics, the most important were age (especially the age group above 65 years old), gender and insurance-type. The organisation of the general practice does not have a significant influence. The number of foreigners in a zipcode area did not have any significant influence on the workload. The patient characteristics are therefore the most important predictors for the workload. The method of calculating the workload can be improved by granting a higher weight to the patient factors. Replication research is necessary to determine if the results are also applicable to other cities with deprived areas.



In chapter 5 a two level model is presented to identify patterns from prescription data of patients older than 18 years, derived from the RNG for whom antibiotics was prescribed. It concerns a longitudinal design in which 125705 prescriptions are nested within 30167 patients in a period of five years (1998-2002). Three research questions will be answered, viz. 1) which pattern, if any can be identified for patients receiving antibiotics; 2) are these patterns stable across time, and do they have specific characteristics? 3) what are the relations with patient characteristics? In order to answer the research questions, a latent class model was applied stratificating the five chapters of the International Classification for Primary Care-system (ICPC), viz. tractus respiratorius, urinary tracts, ear, skin and the rest group. In this patient population of 18 years and older, two to three classes were identified. The three classes can be defined as class 1: ‘no prescriptions’-group, class 2: ‘varied prescriptions’-group and class 3: ‘high prescriptions’-group. With regard to the chapter concerning the ear a two-class model was identified. This is related to the low prevalence of prescribing of antibiotics to patients older than 17 years. Comparing the two most important ICPC-chapters in which most antibiotics were prescribed, viz. tractus respiratorius and urinary tracts, it turns out that 75% of all patients did not receive antibiotics with regard to the tractus respiratorius and that 85% of all patients did not receive antibiotics with regard to the urinary tract. This means that patients with tractus respiratorius problem receive more antibiotic prescriptions than patients with urinary tract problems. The mean number of antibiotic prescriptions in class 2 (‘varied prescriptions’-group) is in both cases (tractus respiratorius and urinary tract) 0.4 per year. So, patients belonging to class 2 get an antibiotic prescription once in two years. In class 3 differences can be seen between the tractus respiratorius and the urinary tract, viz. the number of antibiotic prescribing for urinary tract is higher but the number of patients to whom the antibiotics are prescribed, is lower. We found that between 1998 and 2002 the rates were rather stable over time and that there was also a relation between the rates and patient characteristics (age and gender).

In chapter 6 the efficiency of the reduction of prescribing benzodiazepines using a minimal intervention in the North of the Netherlands (the Province of Groningen) is investigated. The method in order to reduce the use of benzodiazepines concerned a letter of the GP to chronic users. The letter included information about the disadvantages of regular use and the advice to reduce or to stop antibiotic use. The study was carried out in the region East- and North-West Groningen from November 1998 to May 2000. The outcome measure was the sum of the number of Defined Daily Dose (DDD) benzodiazepines in six months. DDD is an international volume-measure for the use of drugs. Among the 56 general practices in East-Groningen, 19 general practices made up the intervention group, while the control group consisted of 37 general practices from East-Groningen and 91 general practices from North-West-Groningen. A three level model was used to answer the research question. This model consists of half-year periods nested within patients and the patients were nested within general practices. The half-year periods were defined as dummies in a fully multivariate model. A reduction of 16% was demonstrated after six months and 14% after one year, controlling for patient characteristics (age and gender) and aggregated prescription characteristics (duration and benzodiazepine-type). In this study it is demonstrated that a substantial decrease of prescribing antibiotics can be realized by a simple intervention using a letter of the GP.



Chapter 7 is a general discussion of the four studies comparing the characteristics of the research in which case the multilevel aspect was the main issue. Comparisons between presented models are discussed. Moreover methodological issues, as the advantages of multilevel models are discussed and the arguments in order to apply multilevel in the four studies, were mentioned. Because patients are nested within the GP and/or general practices, multilevel models are the most suitable in order to answer the research questions presented in this dissertation.

# Samenvatting

***Deze dissertatie beschrijft de toepassing van multilevel analyse op grote databestanden uit de huisartspraktijk. De multilevel methode of methodologie heeft betrekking op de manier waarop de gegevens van de patiënt en huisarts samen in één analyse worden genomen, namelijk patiënten zijn genest onder de huisartsen.***
***In hoofdstuk 1 wordt de ontwikkeling tot deze dissertatie beschreven.***

Hoofdstuk 2 bestaat uit een bespreking van wat multilevel methodologie inhoudt, waarbij de vraagstelling en de datastructuctuur, gebruikelijk bij onderzoek naar de huisartspraktijk, belangrijk is. Vraagstelling zowel als datastructuur hebben betrekking op twee populaties, patiënten en huisartsen. In statistische zin is het begrip 'afhankelijkheid' cruciaal: doordat bij de observaties patiënten genest zijn onder huisartsen ontstaat er een afhankelijkheid tussen de gegevens van patiënten van dezelfde huisarts. Hierdoor zijn meer traditionele analysemethoden, zoals lineaire regressie-analyse, die gebaseerd zijn op de assumptie van onafhankelijke waarnemingen, niet direct toepasbaar. Dit wordt nader toegelicht, waarbij argumenten voor de keuze voor multilevel modellering worden gegeven. Tenslotte worden in dit hoofdstuk de voordelen van het gebruik van multilevelmodellen besproken, zoals het ontleden van de verschillende variantie-bronnen, het uitrekenen van random slopes of dat er voor multilevel modellen minder assumpties nodig zijn in vergelijking met de klassieke ANOVA-modellen. Het hoofdstuk eindigt met de probleemstelling van de hoofdstukken in dit proefschrift, die betrekking heeft op vier gebieden m.b.t. het voorschrijven van geneesmiddelen. In de multiniveau-analyse worden resultaten van huisartsen, of praktijken, aangepast volgens factoren die de patiëntenpopulatie van de huisarts-kenmerken of praktijkkenmerken ('case-mix') zoals diagnose, leeftijd en geslacht. De problematiek van de vier onderzoekingen betreft:

1 De relatie tussen het voorschrijven en de adherentie aan de richtlijnen.
2 De relatie tussen de werkbelasting van de huisarts, en de patiënt en zijn leefomgeving.
3 Het in kaart brengen van het antibiotica-voorschrijven, waarbij rekening wordt gehouden met de diagnostische variatie.
4 Het verminderen van benzodiazepine-voorschrijven in een interventie onderzoek.



In hoofdstuk 3 wordt het begrip globale compliantie gebruikt om in een twee niveau model de variatie tussen patiënten, en tussen huisarts-praktijken, te beschrijven. Globale compliantie wordt omschreven als het voorschrijven van een middel dat in een formularium wordt genoemd. Onderzocht wordt in hoeverre globale compliantie verklaard kan worden met patiënt- en huisartskenmerken. Bij 269067 patiënten van 190 huisartspraktijken in Noord-Nederland werd de globale compliantie bepaald als uitkomstmaat in een twee niveau model. De gemiddelde globale compliantie was 82%. De twee huisartspraktijk-variabelen organisatievorm van de praktijk en urbanisatiegraad zijn gerelateerd aan de globale compliantie. De patiëntkenmerken die gerelateerd zijn aan de globale compliantie zijn de case-mix variabelen leeftijd en geslacht en de naar patiënt-niveau-geaggregeerde-voorschrift variabelen, kosten, volume, verschillende ATC-codes. De totale verklaarde variantie van het model waarin huisartspraktijk variabelen, patiëntkenmerken en variabelen die naar patiënt-niveau zijn geaggregeerd, is 28%.

In hoofdstuk 4 wordt de werkbelasting van de huisarts onderzocht in een model waarin de patiënten genest zijn onder huisartsen en de patiënten ook genest zijn onder bepaalde door postcode geïdentificeerde woongebieden (postcode-gebieden). Dit model wordt een gekruist multiniveau model (cross-classified model) genoemd. Met dit model werd de vraag beantwoord of de zorg voor patiënten in achterstandswijken in Groningen arbeidsintensiever is voor huisartsen dan in niet-achterstandswijken. De werkbelasting werd geoperationaliseerd aan de hand van het aantal voorschriften, het aantal face-to-face contacten en het aantal episoden. De gegevens zijn afkomstig van het Registratie Netwerk Groningen (RNG) en van de grootste zorgverzekeraar in de stad Groningen. De gegevens van de zorgverzekeraar bevatten de prescriptiegevens van 66028 ziekenfondspatiënten ingeschreven bij 70 huisartsen. Wat het RNG betreft zijn 14984 patiënten ( waarvan 54.2% ziekenfondspatiënten zijn) ingeschreven bij 7 huisartsen. Ze zijn gestratificeerd naar verzekeringsvorm. De conclusie luidt dat de werkbelasting hoger is in achterstandswijken. De belangrijkste determinanten van de werkbelasting zijn de patiëntkenmerken leeftijd (speciaal de leeftijdsgroep 65+), geslacht en verzekeringsvorm. De organisatie van de huisartspraktijk speelt een geringe rol. Het aantal allochtonen in een postcodegebied blijkt in deze studie geen eenduidige invloed te hebben op de werkbelasting. De patiëntkenmerken zijn dus de belangrijkste voorspellers van de werkbelasting. Het sterker laten meewegen van patiëntgebonden factoren kan de systematiek van berekenen van de zorgbelasting verbeteren. Replicatieonderzoek is nodig om te bepalen of deze bevindingen ook in andere achterstandsgebieden van (grote) steden van toepassing zijn.



In hoofdstuk 5 wordt met een twee niveau model beoogd patronen te identificeren uit de prescriptiegegevens van antibiotica aan patiënten die ouder dan 18 jaar zijn, afkomstig uit het RNG. Het betreft een longitudinale design waarin 125707 voorschriften zijn genest bij 30167 patiënten over een periode van vijf jaar (1998-2002). Drie onderzoeksvragen zijn beantwoord, te weten: 1) zijn voorschrijfpatronen wat betreft antibiotica te identificeren bij patiënten? ; 2) hebben zulke voorschrijfpatronen, als ze bestaan, bepaalde kenmerken die stabiel zijn in de tijd?; 3) zijn er relaties van deze patronen met patiëntkenmerken? Om deze onderzoeksvragen te beantwoorden is een latente klasse modellering toegepast, waarbij gestratificeerd is naar vijf hoofdstukken van het International Classification for Primary Care (ICPC)-systeem, namelijk: luchtwegen (Tractus respiratorius), urinewegen, oor, huid en de rest-groep. In deze patiënten-populatie van 18 jaar en ouder werden 2 tot 3 klassen geïdentificeerd. De drie klassen zijn te omschrijven als klasse 1: ‘geen voorschriften’ , klasse 2: ‘matig veel voorschriften’ en klasse 3: ‘zeer veel voorschriften’. Voor het ICPC-hoofdstuk ‘oor’ was klasse 3 niet van toepassing. Dit komt door de lage prevalentie in een populatie van 18 jaar en ouder. Vergelijken we de twee belangrijkste ICPC-hoofdstukken, waarvoor de meeste antibiotica worden voorgeschreven, met elkaar, te weten: de Tractus respiratorius en de urinewegen, dan blijkt dat aan drie kwart van alle patiënten geen antibiotica met betrekking tot de luchtwegen werden voorgeschreven en bij 85% van alle patiënten geen antibiotica met betrekking tot urinewegen werden voorgeschreven. Dus er worden minder antibiotica voorgeschreven aan patiënten met een aandoening van de urinewegen dan aan patiënten met een aandoening van de Tractus respiratorius. Het gemiddeld aantal voorgeschreven antibiotica bij de klasse 2 ('matig veel voorschriften'-groep) is bij de Tractus respiratorius evenals bij de urinewegen 0.4 per jaar. Dus dit betekent dat voor de patiëntengroep uit klasse 2 geldt dat gemiddeld in twee jaar een voorschrift antibiotica wordt voorgeschreven. In de klasse 3 zijn verschillen te zien tussen de Tractus respiratorius en de urinewegen, namelijk het aantal voorgeschreven antibiotica bij de urinewegen is hoger, maar de recepten worden aan minder patiënten voorgeschreven. De gevonden schattingen bleken stabiel te zijn tussen tussen 1998 en 2002 en er bleek een relatie te zijn tussen de schattingen en de patiëntkenmerken, leeftijd en geslacht.

In hoofdstuk 6 wordt de doelmatigheid bepaald van een minimale interventie om het voorschrijven van benzodiazepinen te verminderen in de provincie Groningen. Deze interventie bestond uit het versturen van een brief van de eigen huisarts aan chronische gebruikers van benzodiazepinen. De brief bevatte informatie over nadelen van regelmatig gebruik en een advies het gebruik te verminderen of te stoppen. Het onderzoek werd uitgevoerd in de regio Oost- en Noord-West Groningen in de periode november 1998 tot mei 2000. De uitkomstmaat was de som van het aantal 'Defined Daily Dose' (DDD) benzodiazepinen per zes maanden. DDD is een internationaal gehanteerde volumemaat voor medicijngebruik. Van de 56 huisartspraktijken in de regio Oost-Groningen vormden 19 huisartspraktijken de interventiegroep, terwijl de controle-groep bestond uit 37 huisartspraktijken uit Oost-Groningen en 91 huisartspraktijken uit Noord-West Groningen. Een drie niveau model werd gebruikt om de onderzoeksvragen te beantwoorden. Het model bestond uit halfjaarlijkse perioden genest binnen patiënten, en de patiënten waren genest binnen huisartspraktijken. De halfjaarlijkse perioden werden als dummies gedefinieerd in een volledig multivariaat model. Er werd een reductie in voorschrijven aangetoond van 16% na zes maanden en 14% na een jaar, waarbij gecontroleerd werd voor patiëntkenmerken (leeftijd en geslacht) en geaggregeerde voorschriftkenmerken (werkingsduur en benzodizepine-type). Aangetoond wordt in dit onderzoek dat een substantiële afname van het voorschrijven van benzodiazepinen gerealiseerd kan worden met een eenvoudige interventie in de vorm van een brief van de eigen huisarts.

In hoofdstuk 7 worden de vier studies besproken en vergeleken op verschillende aspecten zoals hun onderzoeksvorm. Hierbij staat het multiniveau aspect centraal. Tevens worden de gepresenteerde modellen vergeleken en methodologische discussiepunten zoals de voordelen van multiniveau modellen besproken, alsmede de argumenten om in elk van de vier studies een multiniveau design toe te passen. Omdat patiënten genest zijn onder de huisarts en of huisartspraktijken, zijn multiniveau modellen zeer geschikt om de onderzoeksvragen te beantwoorden die in dit proefschrift gesteld zijn.

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# *Curriculum Vitae*

Roy Edmund Stewart werd geboren op 23 mei 1949 te Paramaribo, Suriname. Na de lagere school en middelbare school, behaalde hij in 1968 zijn diploma aan de Surinaamse Kweekschool om later in Nederland te Zwolle af te studeren aan de Christelijke Pedagogische Academie in 1970.
Hij begon de studie psychologie aan de Rijksuniversiteit Groningen en behaalde in 1987 zijn doctoraalexamen met als afstudeerrichting methodologie.
Tijdens zijn studie heeft hij diverse assistenschappen met betrekking tot methodologie vervuld bij het Rekencentrum, het Centrum voor Energie en Milieukunde, en bij de Faculteit der Medische Wetenschappen, afdeling Sociale Geneeskunde en Medische Psychologie. Van 1993 tot 1999 heeft hij methodologische ondersteuning geboden aan het medicatie- en morbiditeits registratienetwerk Groningen (RNG) van de Disciplinegroep huisartsgeneeskunde, vooral op het gebied van onderzoek naar medicatie, voorschrijfgedrag en polyfarmacie.
Hij heeft verschillende bestuurlijke functies vervuld bij maatschappelijke organisaties, o.a bij het Cultureel Centrum voor Latijns-Amerikanen en is lid geweest van de Minderhedenraad, een adviesorgaan van de gemeente Groningen.
Vanaf 1999 werkt hij als medewerker bij de afdeling Gezondheidswetenschappen van het Universitaire Medisch Centrum Groningen (UMCG). Zijn taak is in eerste instantie methodologische ondersteuning bij promotie- en andere onderzoeken. Daarnaast is hij actief in het wetenschappelijk onderwijs van medische studenten als mentor en geeft hij cursussen met betrekking tot methodologie.

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